THE UNIVERSITY
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Inflammatory Bowel Disease, Steroids and Affective Disorder

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Declaration

This is to certify that that the work contained within has been composed by me and is entirely my own work. No part of this thesis has been submitted for any other degree or professional qualification.

Signed

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Thesis Abstract

Inflammatory Bowel Disease (IBD) is associated with high rates of co morbid depression and anxiety. Corticosteroids, used commonly in IBD, are known to cause psychiatric side-effects. Recent studies show that depression is also associated with raised CRP and IL6. This thesis aims to evaluate which demographic, clinical, medication and immunological factors are predictors of anxiety and depression in IBD.

The IBD, Steroids and Affective Disorder (ISA) study is a cross-sectional study of 578 IBD patients in Edinburgh, UK. Subjects underwent assessment including Hospital Anxiety Depression Scale (HADS) past psychiatric history, steroid medication history, Colitis activity Index (CAI) and Harvey Bradshaw Index (HBI), inflammatory markers including CRP, ESR and White Cell Count, the Medication Adherence Rating Scale (MARS) and Altman Self Rated Mania Scale (ARSM) as well as sociodemographic profile and a past history of IBD phenotype progression and past surgical history.

326 patients with Crohn's Disease and 256 with Ulcerative Colitis (72% of clinic attendees) were recruited. 251 (43%) patients scored 12 or above on the HADS questionnaire. 45% of patients had previously suffered from affective illness. Univariate predictors of affective disorder in IBD included female gender, unemployment, being on incapacity benefit, (all $p<0.0001$), having bowel resections ($p=0.032$), having oral disease ($p=0.03$), being diagnosed before age 18 ($p=0.001$), CAI and HBI scores ($p<0.0001$) and being on corticosteroid medication ($p=0.026$). Inflammatory markers were not predictive of affective disorder. Multivariate independent predictors were female gender, unemployment, incapacity benefit status, HBI, CAI and having been on corticosteroids. Subjects with Anxiety had low adherence scores.

Affective illness remains common in IBD and undertreated. High risk groups can be targeted for screening and treatment and consideration should be given to patients on long term corticosteroids. Improved integrated care models may improve comorbid physical and mental health in these patients.

1.0 Introduction

The Inflammatory Bowel Disease, Steroids and Affective Disorder (ISA) study is a cross sectional study which looks at the relationships between the Inflammatory Bowel Diseases; Crohn's Disease and Ulcerative Colitis and the Affective Disorders; Depression and Anxiety. The central questions in this thesis relate to which social, disease and medication factors (with an emphasis on corticosteroids) may predict Depression and Anxiety in this group.

Inflammatory bowel diseases are severe lifelong diseases of the gut. Their age of onset may be as young as childhood but usually they occur in young adulthood. Due to the improvements in managing these conditions over the last century, they are rarely terminal illnesses and patients may have a normal life expectancy albeit subject to numerous periods of disease relapse. The main clinical features of these illnesses include severe inflammation of the gastrointestinal tract which leads to severe abdominal pain, diorama, rectal bleeding, increased bowel frequency and urgency. Presently there exist several medical and surgical interventions for IBD. Medical treatments primarily serve to reduce inflammation. Surgical interventions include bowel resection and the installation of stoma bags. One of the most common pharmacological treatments are corticosteroids which are the mainstay in acute relapse of the condition, but which may present with several side effects when used in the long term.

Corticosteroid medications have been used in several inflammatory conditions since their discovery in the 1950s. These include asthma, COPD, eczema, arthritis and SLE. Due to their

frequency of use, a considerable literature exists documenting the side effects of these medications. One such side effect which has been noted is the often-sudden change in mental state such as a change in mood or evidence of psychotic symptoms or delirium. Much of the existing literature in this area suggests that this relates to a high dose of these medications.

However, since corticosteroids are only prescribed to patients experiencing severe physical illness, it has thus far not been shown that low mood occurring in such patient groups can be accounted for by the corticosteroid and not by the effects of the physical illness.

Inflammatory Bowel Diseases have been long shown to correlate with high levels of psychiatric illness. Up to 50% of patients experiencing a relapse have been noted to have clinical levels of anxiety or depression. This relationship has been shown in studies since the 1920s where it was initially believed that Ulcerative colitis was itself a psychiatric condition which could be treated with psychoanalysis. While this idea is no longer supported, there remains a question about just why the levels of psychiatric illness are so high in IBD. While in all physical illnesses, levels of concurrent depression are high, IBD appears particularly so and furthermore there exists some evidence that a psychiatric illness or life stress may precipitate relapses of IBD.

A more recent line of enquiry has related to the immunological dysfunction seen in patients with depression. Cytokines such as TNF alpha, IL2, IL6 and IL10 have been shown to be abnormal in patients with clinical depression who do not have any notable inflammatory illness. Coincidently it is these cytokines which are dysregulated in IBD.

Bringing these ideas together, there exists a complicated relationship between IBD, Affective Disorders and corticosteroid medication. Could the high levels of depression in IBD relate to having chronic illness; particularly a lifelong experience of pain, diarrhoea, hospital admissions and surgery? Could the high level of depression relate to the coincidental cytokine disturbance seen in both IBD and depression? Could the high level of depression be accounted for using corticosteroids for the treatment in IBD?

Indeed, all these hypotheses are possible and, as will be seen, all may contribute to the presence of depression and anxiety. While much literature has been dedicated to the area of comorbid medical and psychiatric illness, the cohort in this thesis has been studied over time and thus a prospective as well as cross sectional analysis will be performed. Data from this study will include sociodemographic, symptom, inflammation, medication and psychiatric indices which extends the existing literature.

This thesis is structured commencing with a narrative review about the mental disorder associated with corticosteroids. This will be followed by a review of IBD, its relationship with depression and how this has progressed historically. There will be a background account of Affective Disorders and discussion on their association with other physical illnesses, including new findings in psychoimmunology. Patients with Coeliac disease are used as a control group in this thesis and there will be a brief outline of this. Adherence to medication in this population will be studied as a separate study and act as a stand-alone chapter.

Results are divided into social, disease, medication and psychiatric descriptions of the cohort and then univariate analysis was conducted on which of these factors predict

affective disorders. Finally, multivariate models were constructed to consider which factors acted independently.

The ISA study has only been possible due to the considerable work undertaken by the Gastroenterology Department, University of Edinburgh and the subjects have been recruited from what was an already well studied group.

2.0 Corticosteroids and Mental Disorder

The following chapter explores the evidence for Corticosteroid induced psychiatric illness. Corticosteroid medication is an essential treatment in almost all medical specialties. Psychiatric side effects of corticosteroids may be both common and severe and include psychosis, mania, depression, delirium and dependence. Only a small evidence base exists about susceptibility to and epidemiology of these conditions. Corticosteroid induced psychiatric disorder typically has an acute onset and is dose related. Manic symptoms predominate acutely however long-term use may be associated with depression. Steroid dependence and withdrawal syndromes have been documented. Case reports suggest that a combination of mood stabilizers and antipsychotics may be useful in management severe acute effects.

2.1 Introduction

Corticosteroids were first introduced into medical practice in the late 1940s, since when they have been used by almost all medical specialists as effective treatment for autoimmune and inflammatory conditions. Over 5 million prescriptions are written for corticosteroids in the UK each year, at a cost of over £100 million. (1) About 1% of the general population and as many as 7% of hospitalized patients are receiving oral corticosteroid therapy at any given point in time. (1)

In a community-based study published in 1996, 303 (0.5%) out of 65 786 patients received long-term systemic Glucocorticoids. (2) The most recent study looking at the prevalence of glucocorticoid prescription used The Health Improvement
Network (THIN), a database of electronic medical records from 429 general practices (GPs) including 4 518 753 adult patients across the UK, which showed that an average of 0.75% (95% CI 0.74, 0.75) of the population was prescribed long-term oral Glucocorticoid therapy at any time point. (3)

Importantly, over the past 20 years, long-term oral Glucocorticoid prescriptions have increased by 34%. (3)

Whilst being renowned for important therapeutic actions they can have many adverse effects which must be considered in long term treatment. Physical effects such as osteoporosis, central obesity and immunosuppression are frequent in patients receiving

corticosteroids. Psychiatric effects include alterations in mood, delirium, dementia and psychosis. As corticosteroids have a critical place in the management of chronic disease, psychiatrists should be equipped with the knowledge to recognize and manage corticosteroid induced mental disorder. This chapter describes the epidemiology, clinical presentation and management of these conditions.

2.2 Indications and Pharmacology

There are several forms of corticosteroid medication licensed in the UK, including: betamethasone, cortisone acetate, deflazacort, hydrocortisone, methylprednisolone (prednisolone) and triamcinolone. Each of these drugs has varying degrees of mineralocorticoid and glucocorticoid activity. All the above preparations exist in oral or intramuscular form. Inhaled steroid preparations will not be discussed as there is little evidence that they can induce mental disorder. In a study of 4 518 753 UK adult patients Prednisolone was the most frequently prescribed (92.3% of long-term prescriptions) followed by dexamethasone (3.5%), hydrocortisone (3.3%), betamethasone (0.5%) and prednisone (0.2%). The median daily dosage of prednisolone equivalent over the follow-up was 7.5 (5.0-11.3) mg and the median duration was 215 (126-490) days [vs, respectively, 30 (15-39) mg and 9 (6-10) days for treatments 43 months]. (3)

The main indications for these medications are:

- Suppression of inflammatory and allergic bowel disease;
- chronic or treatment resistant Asthma and COPD;

- Immunosuppression in Acute Lymphoblastic Leukemia, Hodgkin's and non-Hodgkin's disease, and Hormone sensitive breast cancer;
- Palliation of symptomatic end-stage malignant disease;
- Organ transplant rejection;
- Auto-immune (Rheumatic) disease such as Systemic Lupus Erythematosus and Wegners Granulomatosis.

Corticosteroids are rapidly absorbed across the gastro intestinal membrane following oral administration. Peak effects can be observed after 2 hours. The circulating drugs bind extensively to the plasma proteins Corticosteroid Binding Globulin (CBG), albumin and transcortin, with only the unbound portion of a dose active. Systemic prednisolone is quickly distributed into the kidneys, intestines, skin, liver and muscle. Corticosteroids also distribute into the breast milk and cross the placenta. Corticosteroids are predominantly metabolized by the liver to active metabolites then further metabolized to inactive compounds. These inactive metabolites, as well as a small portion of unchanged drug, undergo urinary excretion. The plasma elimination half-life is 1 hour whereas the biological half-life of prednisone is 18—36 hours.

Corticosteroids act as glucocorticoid receptor agonists. On binding, the corticoreceptor-ligand complex translocates itself into the cell nucleus, where it binds to Glucocorticoid Response Elements (GRE) in the promoter region of target genes.

The DNA bound receptor then interacts with basic transcription factors, altering gene expression. There are high concentrations of CBG in specific brain areas such as the

hippocampus and pre-frontal cortex and these can therefore be thought of as a potential mediator of corticosteroid induced psychiatric disorder.

2.3 Chronic disease and corticosteroids

In parallel to the psychiatric side effects of corticosteroid therapy, most chronic medical conditions may be associated with considerable psychiatric morbidity. (5) A primary objective of the psychiatrist is to distinguish between the psychiatric effects of chronic illness and corticosteroids. The 1-year prevalence for ICD-10 depressive episode alone is 3·2% (95% CI 3·0–3·5) and an average of between about 9% and 23% of patients with one or more chronic physical diseases have co-morbid depression. In an international meta-analysis, patients with a variety of chronic physical diseases and co-morbid depression had significantly worse health scores than those with chronic disease alone. (5) There are many potential reasons for this, including physical symptoms such as pain and secondary disability leading to loss of function.

Studies of depression amongst the medically ill almost always fail however to account for possible corticosteroid effects. In patients with severe COPD given 30 mg of prednisolone for 14 days, when lung spirometry and mood state were measured, no changes in spirometry were detected until 7 days of active therapy. However, small but significant reductions in anxiety and depression were measured after 3 days of prednisolone and before any measurable improvement in lung function. This single study is an important part of a small evidence base suggesting that corticosteroids produce a mild sense of wellbeing rather than the wellbeing necessarily being a consequence of physical improvement. (6)

2.4 Classification, Epidemiology and Clinical Features

Psychiatric side effects were first described and classified by Rome and Braceland in 1952 shortly after the initial introduction of corticosteroids into the pharmacopoeia. As can be noted in Table 1, the descriptions of symptoms in 1952 have an implicit hierarchy which places psychosis above “ego” disturbance of a neurotic nature and places these above euphoria. (7)

Table 1: Clinical Classification of Psychological Response to Steroids

Grade	Definition
1	Mild euphoria, lessened fatigue, improved sensation, increased sense of intellectual capacity.
2	Heightened euphoria. Patients are effusive, expansive, volatile, hypomanic, exhibit flight of ideas, impaired judgment, and refractory insomnia.
3	Difference responses to reflecting the ego characteristics of the patient, such as anxiety, phobia, rumination, obsessional preoccupation, hypomania, or depression.
4	Grossly psychotic reaction with hallucinations, delusions, extreme variations in mood.

2.5 Epidemiology

The proportion of patients developing psychiatric symptoms during corticosteroid therapy has been reported to range from 3 to 75 percent, with a weighted average of about 28 percent. (8) Amongst the larger studies, the Boston Collaborative Drug Surveillance Program (9) monitored 718 hospitalized medical patients who received prednisolone, of whom just 21 (3%) had acute psychiatric reactions: in 6 of 463 (1%) patients receiving 40mg prednisolone, 8 of 175 (5%) patients receiving 41-80mg and 7 of those receiving above 80mg (18%). The dose-response trend was significant, but the study was conducted in 1972 and deals with relatively small numbers of affected subjects who underwent only a basic psychiatric screening. Lewis and Smith reported a weighted average 5.7% incidence of severe psychiatric symptoms across 13 studies involving 2555 patients treated with steroids. A review of psychiatric symptoms in cancer patients treated with high-dose corticosteroids noted a 5–10% incidence. (10) Nishimura et al. reviewing treatment episodes in 135 patients with SLE but without overt central nervous system manifestations, observed 14 cases (10.1%) of new-onset DSM-IV disorders, primarily manic episodes (n = 9, 6.5%). (11) A review by Sirois reporting on DSM-IV steroid 'psychosis', found a syndromal breakdown of 35% mania, 28% depression, 12% mixed mania and depression. (12) Recent studies have suggested, however, that the risk of depression increases with prolonged or chronic exposure. Gift et al. found significantly greater self-reported depression scores in 20 patients with chronic obstructive pulmonary disease receiving 20–40 mg/day of prednisone for 10–14 days than in 20 not receiving corticosteroids. (13)

In terms of speed of onset, symptoms appear to develop rapidly. In groups of both patients and healthy subjects, psychiatric symptoms occurred between 3 days and one week. (8, 14, 15, 16) Evidence shows that significantly more women than men (*P* =0.009) develop psychiatric symptoms as a function of corticosteroid treatment. (17)

Prednisolone is the medication most cited to cause psychiatric side effects. In case reports prednisolone was responsible for 37 cases, followed by methylprednisolone, dexamethasone betamethasone, and hydrocortisone. (8) When dose equivalences were calculated, ranging from 5 to 200mg prednisolone per day, a mean dose of 58.3mg per day or more was cited as substantially raising the risk of a psychiatric reaction. This does not mean that psychiatric reactions only occur at higher dosages.

In a population study based on GP records one study identified 109 incident cases of suicide or suicide attempt and 10,220 incident cases of severe neuropsychiatric disorders in a population of 372,696 patients. The incidence of any of these outcomes was 22.2 per 100 person-years at risk for first-course treatments. Compared to people with the same underlying medical disease who were not treated with glucocorticoids, the hazard ratio for suicide or suicide attempt in exposed patients was 6.89 (95% CI=4.52–10.50); for depression, 1.83 (95% CI=1.72–1.94); for mania, 4.35 (95% CI=3.67–5.16); for delirium, confusion, or disorientation, 5.14 (95% CI=4.54–5.82); and for panic disorder, 1.45 (95% CI=1.15–1.85). (3)

In this study it was found that older men were at higher risk of delirium/confusion/disorientation and mania, while younger patients were at higher risk of

suicide or suicide attempt. Patients with a previous history of neuropsychiatric disorders and those treated with higher dosages of glucocorticoids were at greater risk of neuropsychiatric outcomes. (3)

While dosage is not related to the risk of developing mental disturbances, neither dosage nor duration of treatment seem to impact upon the time of onset, duration, severity, or type of mental disturbances and it is unclear whether patients with a history of psychiatric disorder are predisposed to such disturbances. (18)

2.6 Affective Symptoms

The most common psychiatric reaction during glucocorticoid therapy is mood change, which accounts for almost 90 percent of the psychiatric reactions (14, 10) In a review of 56 case studies of psychiatric reactions to steroids, of those reporting mood symptoms (45 cases), mania was observed in 48%, depression in 25%, and a mixed state in 9%. (4)

Reversible mood change can be seen in healthy control subjects after administration of prednisone and dexamethasone. One study showed that 8/12 healthy controls experienced this, with manic symptoms predominating. (20) A further study which looked at methylprednisone in ophthalmology patients, all of whom were free of psychiatric disorder, found that 36% developed mania or depression during high dose steroid treatment. (16)

Studies examining the consequences of low dose steroid treatment have found little or no affective symptomatology (6).

Regarding steroid induced mania, patients typically report sudden euphoric mood, excessive energy, indefatigability and some grandiosity. In addition to the rapid development of mood symptoms, suicidality can be associated with steroid treatment. (19). In addition to mood symptoms patients have been reported to experience sleep disturbances and weight gain.

2.7 Recurrent affective disorder

A further important consideration is whether any such affective disturbance involves one isolated episode or leads on to recurrent disorder. Nine patients whose initial clinical presentation met DSM-IV criteria for a steroid-induced mood disorder were shown in the long term to have a clinical course of bipolar disorder. (21) Seven patients initially developed a manic or hypomanic state with sub-acute onset ranging from 1 to 3 months and six patients had manic episodes accompanied by psychotic features. The proportion of manic episodes relative to total mood episodes of the 9 patients was 66%, suggesting manic predominance. Seven patients had future mood episodes that had no direct relationship to corticosteroid therapy and were preceded by various psychosocial stressors. Four of 5 patients who received future steroids rapidly became manic or hypomanic. Recurrent cases of corticosteroid-induced mood disorder therefore appear to have clinical features such as sub-acute onset, frequent accompanying psychotic features, and similar recurrent episodes in association with psychosocial stressors and corticosteroid use.

2.8 Psychotic Symptoms

In a review of 55 case reports of steroid induced psychiatric disorder, 58% of cases demonstrated psychotic symptoms. (18) In 72% of the cases with psychotic symptoms, they were combined with an affective disorder. Similarly, in a review of 79 case reports there was a 71% incidence of psychotic symptoms with affective symptoms reported in over 75% of these. Hallucinations occurred in 58% of the cases and delusions in 74%. (8)

In a more recent review of 56 case reports, psychotic symptoms were reported in 65% of cases. In eight of these, the development of psychotic symptoms was more clearly associated with the withdrawal, rather than with the administration, of steroids. (19) Interestingly, but perhaps coincidentally, seven of these eight cases occurred in female patients. All eight cases included mood disturbance; 2 with depression, 4 with mania, and 2 with a mixed state.

2.9 Cognitive effects

The cognitive effects of corticosteroid therapy have been seen in patients receiving short term or long-term corticosteroids and relate primarily to declarative or verbal memory. (19)

In one study, patients on corticosteroids had poorer performance on the Rey Auditory Verbal Learning Test (RAVLT), (a measure of declarative memory), the Stroop Color Word Test (a measure of working memory) performance, smaller hippocampal volumes and lower

levels of N-acetyl aspartate (a putative marker of neuronal viability in the temporal lobe region). (22)

Deficits in declarative memory have been observed in subjects receiving as low as 4 to 5 days of dexamethasone or prednisone. (23) A dose-dependent impairment in declarative memory has been reported with high dose (160 mg/day), but not low dose (40 mg/day) hydrocortisone. It appears that these cognitive impairments may be reversed with the reduction or withdrawal of corticosteroids. Similar results for declarative memory deficits are found in persons with Cushing's disease. Such findings are consistent with reductions in hippocampal volume which are correlated with cortisol levels. (24)

2.10 Steroid Dependence and withdrawal

Several case reports suggest that corticosteroids may be abused for their euphoric effects. (25) Typically, this will involve higher doses of oral systemic steroids although there is one report of dependence secondary to a nasal spray. (25)

In a case review, 8 patients out of 11 cases of steroid dependency had a previous psychiatric history (predominantly depressive symptomatology), and 4 had a history of drug or alcohol misuse or dependence. It has been suggested that patients who may request higher steroid doses or who resist dose reduction despite their improving health should be carefully monitored. (25)

In the more recent review of case studies (19), the development of psychiatric symptoms was also associated with the withdrawal of steroids. Corticosteroid withdrawal symptoms generally include depression and fatigue, but mania and delirium have also been reported during dose reduction or discontinuation. Psychiatric symptoms during steroid withdrawal generally improve or resolve when corticosteroids are re-introduced.

2.11 Cushing's disease and psychiatric disorder

Cushing's syndrome relates to the multi-organ over exposure of iatrogenic or endogenous corticosteroid and is associated with a variety of psychiatric and psychological disturbances. In one study examining 43 patients before and after treatment for Cushing's, psychopathology was observed in a considerable number. Only 8 patients of 43 with active Cushing's syndrome (19%) were without psychiatric symptoms. Psychiatric diagnoses included: neurotic depression in 20 (46%), possible neurotic depression in 1 (2%), reactive depression in 6 (14%), and non-specific neurotic symptoms in 8 (19%). Psychoses were suspected in 3 of the patients who were depressed, but none of the 43 patients with active Cushing's syndrome had a definite diagnosis of Schizophrenia, Mania, Obsessive Compulsive Disorder or Generalised Anxiety Disorder.

After treatment in 25 patients, when cortisol levels had been substantially reduced (to within normal limits in 88% of them), the percentage rated as psychiatrically asymptomatic increased from 19% to 68%. Scores for depression and anxiety showed significant improvements after treatment for Cushing's syndrome and Eysenck Personality Inventory assessments showed a significant improvement in neuroticism score. (26)

2.12 Treatment of Corticosteroid induced psychiatric disorder

There is a very limited literature on the treatment of corticosteroid induced mental disorder, although it can be noted that psychiatric symptoms generally resolve with discontinuation of the medication. In one review of the literature, tapering the dose of steroids alone appears to be effective up to 90% cases. (19) Case studies also suggest that switching steroids may be of value. (27) The primary objective in managing these conditions is to balance the relative risk of psychiatric disturbance against the medical consequences of withdrawing the steroid.

The management of corticosteroid induced psychiatric disorder can otherwise be largely divided into managing an acute psychotic/manic episode versus managing long term depressive symptoms and dependency. Although little evidence exists either way, it can be assumed that severe behavioral disturbance should be managed as per protocol - symptomatically with appropriate doses of benzodiazepines and antipsychotics.

In terms of managing acute psychotic/manic episodes one study found that of 27 patients treated with lithium carbonate prophylactically, none developed severe mood symptoms while receiving corticosteroids. However, six out of 44 patients (14%) not receiving lithium developed mania or depression. (28) Antipsychotics, specifically haloperidol, risperidone and olanzapine, are noted from case reports to be useful in mania, mixed affective states, psychosis and delirium. A further case report suggested the successful use of low-dose

olanzapine (2.5 mg/day) for severe mood swings and suicidal ideation in a patient with asthma on chronic prednisolone therapy.

With regard to depressive symptoms, several case reports have demonstrated some evidence with lithium following the onset of depressive symptoms. Carbemazepine has been reported to be useful in managing both manic and depressive symptoms secondary to corticosteroids. (29) There appears to be little benefit from the use of tricyclic antidepressants and in fact, a worsening of neuropsychiatric symptoms has been reported. (14) Case reports have been published describing the successful treatment of steroid-induced depression with sertraline, fluvoxamine, and fluoxetine. One such report supports the use of a combination of an antidepressant and antipsychotic in the treatment of steroid-induced psychotic depression (30). Case reports are noted to suggest the effectiveness of benzodiazepines, in the management of specific steroid-induced symptoms as insomnia and anxiety

2.13 Conclusions

Above all, the literature on the psychiatric adverse effects of corticosteroids is limited and larger studies on medically ill populations need to be carried out. Clinical practice continues to be informed by case reports despite over 50 years of awareness of these problems. There exists a great opportunity for future research to find predictors of steroid response including their genetic and neuroimaging antecedents and the literature could be enhanced with prospective studies and clinical trials.

The ICD 10 codes steroid induced psychiatric disorder under F55.5 “Abuse of non-dependence-producing substances “Steroids or Hormones”. No distinction is made about type or chronicity of symptoms. Arguably it may be more useful to classify steroids induced psychiatric disorder under F19.-Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances. Corticosteroid induced psychiatric disorder can pragmatically be classified at present as described in table 2.

Table 2 Possible classificatory system for Steroid induced psychiatric illness

Type	Subtype	ICD 10 Coding: F55.5 Abuse of non-dependence-producing substances "steroids or hormones" F19.-Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances
Acute corticosteroid syndrome	Hypomanic/Manic type with or without psychotic symptoms	F19.55 Predominantly manic symptoms
	Depressive type with or without psychotic feature	F19.54 Predominantly depressive symptoms
	Mixed affective type with or without psychotic features	F19.56 Mixed
	Psychotic Type	F19.50 Schizophrenia-like F19.51 Predominantly delusional F19.52 Predominantly hallucinatory F19.53 Predominantly polymorphic
Chronic corticosteroid syndrome	Depression	As F30-F39 Mood (affective) disorders
	Recurrent affective disorder either depressive type or bipolar type	As F30-F39 Mood (affective) disorders
	Chronic cognitive impairment	Unknown
Corticosteroid dependence	Dependence currently active use	F19.24 Currently using the substance (active dependence)
	Withdrawal syndrome	F19.30 Withdrawal state: Uncomplicated

Regarding the acute corticosteroid syndrome, the clinical presentation can be diverse, but the severity of the symptoms appears to be dose dependent and they tend to occur within the first week of steroid administration. Affective symptoms are most common and a hypomanic/manic presentation is most likely. Some patients appear to have sub clinical hypomanic symptoms which they do not report. Symptoms resolve in most cases on discontinuation of the steroid. Cases are best treated with a mixture of a mood stabilizer (possibly prophylactically) and antipsychotic.

With regards to chronic steroid syndrome, the merits of continuation of the steroid must be considered and a small literature suggests that depression in this group can be managed with an SSRI.

In patients who are on long term steroids, a dependence and withdrawal syndrome may be seen. No evidence exists as to how this should be managed but again negotiation should occur between the clinicians and the patient on the need for steroids and a gradual tapering of dose should be considered.

Presently it is not known whether individuals have idiosyncratic reaction to steroids or that, given a high enough dose everyone would suffer some mental disturbance. There is a suggestion that those with a previous affective disorder or a family history may be more susceptible to the adverse effects of steroids. If as many as 27% of those on high dose steroids suffer psychiatric symptoms, it is surprising that millions of patients do not present to psychiatric services.

In conclusion the available literature on corticosteroid induced psychiatric illness is limited. There exist two important questions which have not been answered. Firstly, can anyone incur a psychiatric reaction to corticosteroids and secondly in chronic corticosteroid use, can controlling for the effect of a physical illness demonstrate an independent depressogenic effect of the corticosteroid.

3.0 Inflammatory Bowel Diseases and Coeliac Disease

The following chapter will address 3 key areas with regards to Inflammatory Bowel Diseases and give an overview of coeliac disease. Firstly, there will be a description of the clinical features, aetiology and treatment of IBD. Detailing of these features is necessary to support the hypothesis that some of these may predict psychiatric outcomes. Secondly there will be an account of the historical context of IBD and associations with affective disorders and thirdly there will be a review of existing literature which details the relationship between affective disorders and IBD. As patients with coeliac disease will be used as a control population a brief overview of coeliac disease will be given.

3.1 Clinical features, aetiology and treatment of Inflammatory Bowel Diseases

3.1.1 Introduction

Inflammatory Bowel Disease (IBD) consists of two principal diagnoses: Crohn's Disease (CD) and Ulcerative Colitis (UC). A third, rarer, diagnosis Indeterminate Colitis lies clinically and histologically between these two and represents a diagnostic intermediary.
Inflammatory bowel diseases consist of idiopathic, chronic, nonspecific inflammation of the gastrointestinal tract. They are persistently relapsing intestinal inflammatory conditions with a typical onset in young adulthood and with an unpredictable course.
Pathogenesis of IBD is considered to involve a complex interplay between genetic, environmental, microbial, and immune factors. Lifelong medication has remained the basis of IBD management along with surgery.

Here, both main diagnoses will be discussed in relation to their presentation, main symptoms, clinical course and prognosis as it will apply to possible consequent psychological or psychiatric symptoms. The immunology, genetics and treatment of both conditions will be discussed together with reference to psychiatric issues.

3.1.2 Crohn's Disease

Crohn's disease was first described in 1932 by American gastroenterologist Burrill Bernard Crohn, who described a series of patients with inflammation of the terminal ileum.

With regards to epidemiology, the lifetime risk of Crohn's from population studies in developed countries has been shown to vary from 28 to 213 per 100,000. (31) In international studies: north-south, east-west, and urban-rural gradients for incidence and prevalence of Crohn's disease have been identified. (32, 33)

Crohn's disease has a bimodal distribution in terms of age of onset; firstly, adolescents and young adults and then adults aged 50-70 years. Early onset can range from 0.2-9.0/100,000 per year and late onset from 1.5-8.0/100,000 per year. (33) Males and females are equally affected. Early tobacco use significantly increases the risk of developing the disorder. (35)

Twin studies show a concordance of greater than 55% for Crohn's disease. (34) Approximately 12% of patients with Crohn's Disease have a family history of the disease. (36)

3.1.2.1 Classification

Crohn's disease may be categorized by the specific area of the gastro intestinal tract affected. Around 20% of cases are uniquely colonic, 30% are ileal and 50% both ileal and

colonic. While the disease can affect any part of the digestive tract, affected individuals rarely fall outside these three classifications. (37)

Categorization of Crohn's disease has been both by the Vienna Classification and subsequently by the Montreal Classification. (38) The Vienna classification describes stricturing, penetrating, and inflammatory subtypes of disease. The inability of the Vienna classification to allow upper gastrointestinal disease to coexist with more distal disease has led to the Montreal classification. The importance of this in the context of this thesis is that subjects in this study have been categorized in both systems at the time of their primary assessment. (38)

Vienna and Montreal Classification systems (38)

	Vienna	**Montreal**
Age at Diagnosis	A1 below 40y	A1 Below 16y
	A2 above 40y	A2 between 17 and 40y
		A3 above 40y
Location	L1 ileal	L1 ileal
	L2 colonic	L2 colonic
	L3 ileocolonic	L3 ileocolonic
	L4 upper	L4 isolated upper disease
Behaviour	B1 non stricturing, non penetrating	B1 non stricturing, non penetrating
	B2 stricturing	B2 stricturing
	B3 penetrating	B3 penetrating
		P perianal disease modifier

3.1.2.2 Clinical Presentation

The hallmark of Crohn's disease is the constellation of gastrointestinal symptoms. The main clinical symptoms are contained in the table below. (39)

Gastrointestinal symptoms
- Abdominal pain - Diarrhea and rectal bleeding. (Type of Diarrhea relates to the part of the small intestine or colon involved. Ileitis typically results in large-volume, watery feces. Colitis may result in a smaller volume of feces of higher frequency.) - Faecal consistency ranging from solid to watery. - Up to 20 bowel movements per day are reported and may need to awaken at night to defecate. In the setting of severe Crohn's colitis, bleeding may be copious - Flatulence and bloating - Vomiting and nausea may be present and may be a sign of small bowel obstruction due to severe stenosis - Perianal pruritis or pain which may be suggestive of inflammation, fistulization or abscess around the anal area or anal fissure - Perianal skin tags - Faecal incontinence - Aphthous ulcers in the mouth - Dysphagia, upper abdominal pain, and vomiting may be present when the esophagus and stomach are involved
Extra intestinal symptoms
- Pyrexia - Cachexia - Uveitis - Episcleritis - Seronegative spondyloarthropathy affecting knee, shoulder, hands, feet

- Ankylosing spondylitis.
- Erythema nodosum
- Pyoderma gangrenosum
- Autoimmune hemolytic anemia
- Finger clubbing
- Osteoporosis
- Seizures, cerebrovascular events, headaches and peripheral neuropathy reported in up to 33.2% of patients in one study

3.1.2.3 Diagnosis

The diagnosis of Crohn's disease is based upon clinical history combined with serological and radiological investigations. Serological investigations include status of Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP). (39) Faecal calprotectin is a biochemical measurement of the protein calprotectin in the stool. Elevated faecal calprotectin indicates the migration of neutrophils to the intestinal mucosa, which occurs during intestinal inflammation and is used as a diagnostic tool and marker of severity of disease. (39)

3.1.2.4 Surgical intervention

Surgery remains an effective and often first line option in the management of Crohn's Disease and may also be required for complications such as obstructions, fistulas and/or abscesses, or non-response to pharmacotherapy. After the first surgery, Crohn's may appear at the site of the resection. After a resection, strictures may form leading to obstruction. The likelihood of resection increases with further resections. (40)

3.1.2.5 Prognosis

The clinical course of Crohn's Disease can be variable and is difficult to predict based on the presentation at diagnosis. In one systematic review approximately one-third of the patients had ileitis, colitis, or ileocolitis at the time of diagnosis and the disease location remained generally stable over time. Approximately ten percent of patients have prolonged clinical remission. Annual incidence of hospitalizations was 20 %. Half of the patients required surgery within 10 years of diagnosis. Risk of postoperative recurrence was 44 – 55 % after 10 years. (41, 42, 43)

The probability of being without relapse from one study is 22 % after 5 years to 12 % after 10 years. Risk of a continuous disease activity without clinical remissions is around 4 % after 5 years and 1 % after 10 years. Half of the patients with active disease could expect to have a full year in remission within 3 years. (43)

3.1.3 Ulcerative Colitis

Ulcerative Colitis was first named in 1857 by Samuel Wilks but it was not till a century later that an understanding of pathogenesis began.

3.1.3.1 Epidemiology

The incidence of ulcerative colitis is approximately 10–12 cases per 100,000 per year, with a peak occurring between 15 and 25. Lifetime prevalence is 1 per 1000. There is thought to be a bimodal distribution in age of onset, with a second peak in incidence occurring in the 6th decade of life. The disease affects females more than males (43)

The geographic distribution of Ulcerative Colitis shows the highest incidences in the United States, Canada, the United Kingdom, and Scandinavia. Higher incidences are seen in northern locations compared to southern locations in Europe and the United States. (32)

3.1.3.2 Gastrointestinal symptoms and classification

The main symptomatic presentation is of diarrhea mixed with blood and mucus. Comorbid signs include weight loss and blood on rectal examination. The disease is usually accompanied with different degrees of abdominal pain.

The disease is classified by the extent of colonic involvement: Distal colitis, Proctitis, Proctosigmoiditis, Left-sided colitis: Involvement of the descending colon up to the splenic flexure and the beginning of the transverse colon, Extensive colitis, Pancolitis: Involvement of the entire colon, extending from the rectum to the cecum up to small intestine
In addition to the extent of involvement, UC patients may also be characterized by the severity of their disease.

Mild disease correlates with fewer than four stools daily, with or without blood, no systemic signs of toxicity, and a normal erythrocyte sedimentation rate (ESR). There may be mild abdominal pain or cramping.

Moderate disease correlates with more than four stools daily, but with minimal signs of toxicity. Patients may display anemia moderate abdominal pain, and low-grade fever

Severe disease, with more than six bloody stools a day, and evidence of toxicity as demonstrated by fever, tachycardia, anemia or an elevated ESR.

Fulminant disease includes more than ten bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilation. Possible toxic megacolon

3.1.3.3 Extraintestinal features

In addition to gastrointestinal features, inflammation may occur in different systems including; aphthous ulcers of the mouth, Iritis or uveitis, Episcleritis, Primary sclerosing cholangitis, Seronegative arthritis, Ankylosing spondylitis, Sacroiliitis, Erythema nodosum or Pyoderma gangrenosum.

3.1.3.4 Diagnosis

Diagnosis is based on serological and radiological evidence which would include: anaemia, abdominal x-ray, ESR, CRP, lymphocytic infiltration of mucosa on biopsy, colonoscopy or flexible sigmoidoscopy.

The Montreal classification assesses extent of disease and severity of symptoms, which have important prognostic value. The extent of disease is classified as endoscopic mucosal changes limited to the rectum (E1), left side of the colon, (E2) and beyond the splenic flexure (E3). Symptom severity score ranges from none (S0) to severe systemic manifestations (S3).

Montreal Classification of UC (45)

Extent/severity		**Anatomy/definition**
E1	Ulcerative proctitis	Involvement limited to rectum
E2	Left sided UC (distal UC)	Involvement limited to a portion of the colorectum distal to the splenic flexure
E3	Extensive UC	Involvement extens proximal to the splenic flexure
S0	Clinical remission	Asymptomatic
S1	Mild UC	Passage of four or fewer stools/day with or without blood, absence of systemic illness and normal inflammatory markers
S2	Moderate UC	Passage of more than 4 stools each day with evidence of systemic toxicity
S3	Severe UC	Passage of at least 6 bloody stools each day and markers of haemocompromise

3.1.3.5 Surgical intervention

Unlike Crohn's disease, ulcerative colitis can be cured by colectomy. In a population-based study (48) extensive colitis at presentation was found to be an independent predictor of

colectomy at both 1 year and 10 years after diagnosis. Colectomy rates in UC patients vary from 6% in one year to 8.7% over 10 years. (49, 50)

3.1.4 The Aetiology of Inflammatory Bowel Disease

Inflammatory bowel diseases are of multifactorial aetiology comprising both genetic and environmental causative factors. While diet, breastfeeding and smoking are all cited risk factor for the diseases, in this thesis emphasis will be placed upon genetic and immunological factors in as far as they relate to pathological changes seen in depression.

3.1.4.1 Immunological changes in IBD

Cytokines have been directly implicated in the pathogenesis of IBD in recent genetic and immunological studies, and have a crucial role in controlling intestinal inflammation and the associated clinical symptoms of IBD (51) The role of cytokines is also highlighted by the blockade of tumour necrosis factor (TNF) being commonly used as a standard therapy for IBD (52)

Interleukin‐6 (IL‐6) induces acute-phase proteins by the liver, whereas TNF is implicated in development of arthritis and cachexia. (53) Further studies have identified IBD risk loci that contain genes which encode cytokines (e.g. IL‐2, IL‐21, interferon‐γ (IFNγ), IL‐10 and IL‐27). IL‐6 production by lamina propria macrophages and CD4+ T cells is increased in experimental colitis and in patients with IBD (54)

The production of both membrane-bound and soluble TNF by lamina propria mononuclear cells is markedly augmented in patients with IBD. (55)

3.1.4.2 The Genetics of Inflammatory Bowel Disease

While IBD is likely to be caused by multiple genes of small effect size, several candidate genes have been shown to have a larger effect, but these contribute to a small amount of the genetic variance of the illness. Crohn's disease shows high concordance for monozygotic twins of around 36% whereas Ulcerative Colitis has a concordance of around 16%. A family history of IBD may be seen in up to 30% of patients. (60)

Promising candidate genes have been discovered for IBD including the *NOD2/CARD15* gene (57) Germline variation of *NOD2/CARD15* has remained the strongest genetic determinant of genetic CD susceptibility with an odds ratio of 3.99 in GWAS meta-analysis (57).

3.1.5 Treatment in Inflammatory Bowel Disease

The main treatments for Crohn's disease involve either medical or surgical approaches as well as diet and lifestyle management. Here there will be specific focus on two principal medical therapies; corticosteroid medication and anti TNF alpha immunoglobulin.

The treatment for acute relapse involves aminosalicylate anti-inflammatory drugs and corticosteroids. Alternatives include aminosalicylates alone though many patients require immunosuppressive drugs. (58)

3.1.5.1 Main Pharmacotherapy

Below is a table outlining the main pharmacological agents for treatment in IBD and NICE guideline recommendations for both management of an acute episode and remission maintenance. (58)

Class	Examples (Brand Names)	NICE Guidelines Recommendations
Aminosalicylates	Mesalazine, mesalamine, or 5-ASA (Apriso, Asacol, Pentasa, Mezavant, Lialda, and Salofalk) Sulfasalazine (Azulfidine). Balsalazide (Colazal or Colazide)	Induction of remission in acute episode 1.2.4 In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period.
Corticosteroids	Cortisone Prednisolone Hydrocortisone Methylprednisolone Beclomethasone Budesonide	Induction of remission in acute episode 1.2.2 Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. 1.2.3 In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that

		budesonide is less effective than a conventional glucocorticosteroid but may have fewer side effects. <u>Maintenance of remission treatment</u> 1.3.7 Do not offer a conventional glucocorticosteroid or budesonide to maintain remission. 1.2.5 Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations. 1.2.6 Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission
Immunoglobulins	Infliximab, Adalimumab (Hummira)	1.2.12 Infliximab and adalimumab, are recommended as treatment options for adults with severe active Crohn's disease (see 1.2.17) whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter.
Other Immunosuppressants	Mercaptopurine, (6-Mercaptopurine, 6-MP and Purinethol) Azathioprine (Imuran, Azasan or Azamun) Methotrexate, Cyclosporine	<u>Induction of remission in acute episode</u> 1.2.7 Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if: there are two or more inflammatory exacerbations in a 12-month period, or the glucocorticosteroid dose cannot be tapered. 1.2.9 Consider adding methotrexate to a conventional glucocorticosteroid or budesonideto induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if: there are two or more inflammatory exacerbations in a 12-month period, or the glucocorticosteroid dose cannot be tapered. <u>Maintenance of remission treatment</u> 1.3.4 Offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission. 1.3.5 Consider azathioprine or mercaptopurine to maintain remission in people who have not previously received these drugs (particularly those with adverse prognostic factors such as early age of onset, perianal disease, glucocorticosteroid use at presentation and severe presentations). 1.3.6 Consider methotrexate to maintain remission only in people who: needed methotrexate to induce remission, or have tried but did not tolerate azathioprine or mercaptopurine for maintenance or have contraindications to azathioprine or mercaptopurine

3.1.5.2 Corticosteroid therapy

Historically the most important treatment for an acute relapse of IBD involves use of corticosteroid medication.

The most recent Cochrane review looking at the efficacy and safety of traditional corticosteroids for induction of remission in CD included RCTs with control groups receiving either placebo or 5-aminosalicylates (5-ASA). (59) Comparing corticosteroids to placebo and comparing corticosteroids to 5-ASA; Corticosteroids were found to be significantly more effective than placebo at inducing remission in CD (RR 1.99; 95% CI 1.51 to 2.64; $P < 0.00001$) and that Corticosteroids were found to be more effective than 5-ASA at inducing remission in studies with long follow-up duration (i.e. > 15 weeks; RR 1.65; 95% CI 1.33 to 2.03; $P < 0.00001$). Psychiatric consequences of corticosteroid medications were not documented in the final review or in any of the individual studies therein. (59)

The review concluded that Corticosteroids are effective for induction of remission in patients with CD, particularly when used for more than 15 weeks. (59)

The second question which is relevant to this thesis is the Cochrane review on efficacy of corticosteroids for maintenance therapy and whether there is an identifiable subgroup of Crohn's disease patients, such as those in whom therapy cannot be successfully tapered, who might benefit from such treatment. (59)

This review concluded that the use of conventional systemic corticosteroids in patients with clinically quiescent Crohn's disease does not appear to reduce the risk of relapse over a 24-month period of follow-up.

The natural history of response to corticosteroid therapy was specifically investigated in population-based studies. (60) In 196 patients over 10 years after a median follow-up of 3.4 years, 56 % had received at least one systemic steroid treatment course, of whom 84 % received their first steroid course within the first year after diagnosis. The median duration of treatment was 84 days (range, 5 – 299). (60) Among the patients who received steroids, 48 % achieved clinical remission, 32 % had partial clinical response, and 20 % did not respond to corticosteroid therapy. At the end of follow-up, 48 patients (44 %) had prolonged steroid response, 39 (36 %) were steroid dependent, and 22 (20 %) had steroid resistance. A total of 21% patients required surgical resection, including 26 % of patients with steroid dependency and 59 % of patients with primary non-response to steroids. (60)

In a further study of 171 patients with Crohn’ s disease, 43% received corticosteroid therapy— 58% achieved complete remission, 26 % had partial response, and 16 % had no response after 30 days (59)

The relevance of these studies for this thesis is that a significant number of patients will be treated with corticosteroid medications in any given year and that these medications remain central in the treatment of IBD.

3.1.5.3 Anti TNF immunoglobulins

A more recent edition to the therapeutic arsenal in Crohn's disease is the use of anti TNF alpha immunoglobulin. Anti-TNF-α agents have been shown to be effective for the induction of remission in Crohn's disease. In the Cochrane review on anti TNF agents in Crohn's Disease, four different anti-TNF-α agents were evaluated (infliximab in 3 studies, CDP571 in 3 studies, adalimumab in 2 studies, and certolizumab in 1 study). There is evidence from three randomized controlled trials that infliximab maintained clinical remission (RR 2.50; 95% CI 1.64 to 3.80), maintains clinical response (RR 1.66; 95% CI 1.00 to 2.76), has corticosteroid-sparing effects (RR 3.13; 95% CI 1.25 to 7.81), and maintains fistula healing (RR 1.87; 95% CI 1.15 to 3.04) in patients with Crohn's disease with a response to infliximab induction therapy. There is evidence that adalimumab maintains clinical remission, clinical response, and has corticosteroid-sparing effects in patients with Crohn's disease who have responded or entered remission with adalimumab induction therapy. (61)

In the Cochrane review, in patients with moderate to severe ulcerative colitis whose disease was refractory to conventional treatment using corticosteroids and/or immunosuppressive agents, infliximab was more effective than placebo in inducing clinical remission at 8 weeks. A single infusion of infliximab was also more effective than placebo in reducing the need for colectomy within 90 days after infusion (RR 0.44, 95% CI 0.22 to 0.87). (62)

The review concluded that in patients with moderate to severe ulcerative colitis whose disease is refractory to conventional treatment using corticosteroids and/or

immunosuppressive agents, infliximab is effective in inducing clinical remission and reducing the need for colectomy at least in the short term.

3.1.5.4 Conclusion

This section attempts to summarize the main features of IBD and its treatment. The clinical features of IBD can be chronic, distressing and disabling. Awareness that the life long course of IBD would be distressing and how the symptoms may preclude a sufferer from education and employment can be extrapolated. Furthermore, an awareness of the complexity of both surgical and medication treatment leads to an understanding of the high psychological burden of patients with IBD. This thesis will try and use indices to measure the severity of IBD in the cohort and this chapter demonstrates that this could be done by physical symptoms, inflammatory markers, surgical history and medication.

3.2 Psychiatry and Inflammatory Bowel Disease: A Historical Perspective

Psychiatric illnesses have historically depended on varied etiological paradigms including the socio-cultural, psychoanalytic and bio-medical. However, the rise of pathology and molecular medicine has moved physical illnesses from the realms of speculation to firm scientific understanding.

Physical and psychiatric illnesses converge in psychosomatic medicine.

The term psychosomatic may have differing meanings but here it will be taken to mean the way in which mental phenomena or experience may lead to biological processes or disease.

In the 20th Century, the rise of the biomedical model has shifted "psychosomatic" illnesses from more psychiatric understanding to a more medical one. An example of this is Inflammatory Bowel Disease (IBD) which, during the 20th century, has been a psychosomatic illness due to a perceived impact of social and psychological factors on the somatic disease process.

Inflammatory Bowel Diseases comprising Crohn's Disease (CD) and Ulcerative Colitis (UC) have a diagnosis based upon colonoscopy or endoscopy aided by biopsy and raised inflammatory markers.

The interest in IBD as a psychosomatic illness derives from the fact that early observations of the condition seemed to suggest that life events, stress or personality type predisposed to the disease. Consequently, there is a substantial literature from both gastroenterologists and psychiatrists as to the basis for this apparent association.

This chapter will review the historical influences which have shaped the understanding of IBD and its relationship to psychiatry.

3.2.1 Early Psychosomatic Theory

The 20th century has produced several important paradigms in psychiatry. Psychoanalytic theory provided the pre-eminent aetiological model of mental illness in general, based on the principles of unconscious thought and childhood development. The biomedical model rose with the psychopharmacological discoveries of the 1950s. Latter-day advances in genetics and neuroimaging have supported the biological paradigm which predominates today as the model of aetiology in psychiatric illness.

What we might call “psychosomatic” problems, now most often referred to as ‘functional’ or medically unexplained symptoms, appeared in the psychiatric lexicon at the time of Freud and Charcot

Franz Alexander described disturbances of the vegetative functions of the body that were the result of a variety of etiological factors both organic and psychological in nature, noting that the impaired vegetative function of the body does not resolve the psychological stress which an individual experience. Thus, a psychosomatic symptom (a physical symptom

secondary to an environmental stress) is distinct from a conversion symptom which he argued allowed resolution of that stressor. (63)

The progress in physiology in the 20th century allowed the study of physical symptoms to gain more medical acceptance than psychiatric symptoms. Thus, the history of psychosomatics in the 20th century evolved differently to psychiatry with respect to major mental illnesses.

3.2.2 The Brain-Gut Axis

The so-called brain gut axis can be understood by the nervous supply of the gut. The vagus and splanchnic nerves supply the small intestine and proximal colon, whereas the pelvic nerves provide input to the colon and anal sphincter.

The concept that the brain and the body can communicate in a bidirectional fashion is illustrated by early work of Henry Cotton an American psychiatrist working at the beginning of the 20th century. Based on the observation that patients with high fever were delusional or hallucinating, Cotton followed the emerging medical theory of infection-based psychological disorders and extrapolated this into pulling patients' teeth as they were suspected of harboring infections. If a cure was not achieved after these procedures, he would resect other organs including stomachs and especially colons. His publications tell us that he resected many patients' colons and that their mental symptoms improved greatly as a consequence with cure rates of 85%. (64)

A more important early study of brain gut interaction comes from the pioneering work of Stewart and Harold G. Wolf, who published an acclaimed work "Human Gastric Function"

based on their observations of a patient known as Tom. (65) As a nine-year-old boy Tom's father brought home some hot soup in a beer bucket. Thinking it was beer, Tom took a swig and burned his oesophagus such that physicians could not keep it open as it healed. For 47 years Tom fed himself through an opening surgeons made in his abdominal wall. As a proud man who had always supported his family, Drs. Wolf and Wolf asked Tom to better his lot and serve as an experimental subject. Wolf and Wolf were able to inform psychosomatic medicine in several important ways. For example, when Tom was frightened both his face and his stomach lining turned pale. When Tom was depressed, his stomach lining, which usually reddened and increased its secretion of acid after a dose of beef, hardly responded at all to such feeding. When Tom became angry, his face reddened and so did his stomach. Significantly, anxiety increased the amount of blood in the stomach membrane and the amount of acid secretion. (65)

Such observations brought credibility to the idea that emotions could directly affect the gut. This would not be replicated in any other mental condition until the advent of functional neuroimaging at the end of the 20th century. However, such observations took place at a time when the psychoanalytic model was at a height just four years after the death of Freud.

Crohn's Disease had yet to be described but there were already many accounts of how stress or emotion could relate to Ulcerative Colitis.

3.2.3 A Psychoanalytic model of Ulcerative Colitis

Ulcerative Colitis was first described in 1859 but even a century later its aetiology was described as "obscure" by the American Gastroenterology Association (66) In 1930 Cecil D

Murray, published a paper claiming that psychological factors were important in ulcerative colitis. Groen and Van de Valk (67) description of this process is highly reminiscent of Freudian conversion theory:

- Certain individuals have a psychological makeup that renders them more vulnerable to conflicts threatening their emotional security.
- Exacerbations of colitis are brought on by an emotional conflict in which the individual is humiliated or defeated emotionally.
- Such persons do not respond to the emotional stimulus by action or words. The resulting emotional conflict produces the changes in the colonic mucosa, which are responsible for the clinical and pathological signs of ulcerative colitis.

Case reports by psychiatrists allude to the ‘confession’ of 'interhuman conflicts' in the immediate period before an attack of the disease (66). Other authors, some using the Rorschach test, claimed that patients with Ulcerative Colitis were “infantile, dependent, passive, egocentric, hesitant, and uncertain” and even suggested 'one may often recognize a colitis patient in the wards by the neat way he wears his pyjamas' (68, 69)

When further research was conducted the limits of the psychodynamic model were reached. While a loose theory about the effect of stress or conflict on the gut appeared valuable, several important questions remained. Did specific conflicts relate to specific symptoms? A paper in 1955 concluded that “to lump together as causes of diarrhoea; anger, resentment, guilt, humiliation, anxiety, and conflict, is to reduce to relative ineffectiveness pertinent psychodynamic formulations.” (70)

A second key question related to understanding the pathogenesis of symptoms. Karush et al sought to do so as until then “psychological descriptions of the emotional states associated with the physiological changes have not proven to be satisfactory psychodynamic formulations” (70) In this paper colonic propulsion was measured by the insertion of three balloons rectally, while salivary flow was measured by a suction cup placed on the buccal mucosa. The analysis sessions were recorded and instances of emotion were chronologically correlated with gut motility and salivary production. The authors noted findings from 6 cases. In one “colonic activity of an intense, segmental, nonpropulsive nature was accompanied by a conscious, fearful attitude, or, more frequently, unconscious fear. The unconscious fear was aroused either by sexual desire inhibited by fear of sex as violence.” In a fifteen-year-old girl “a severe attack of abdominal cramps appeared as she told of her parents' threats of disaster for sexual transgression. The onset of her illness coincided with a tremendous increase in guilty fear because of compulsive masturbation.” The authors concluded that “The outstanding characteristic was dependence upon a magical, omnipotent authority, not merely for cure of the illness, but for resolution of conflicts about aggressive rage.” Unfortunately, less attention in the discussion related to the possible psychological effects of placing three balloons in the rectum. (70)

The 1950s were also a time for major pharmacological advance and ACTH and Corticosteroids were both introduced successfully for the treatment of Ulcerative Colitis. (71) This was greeted with some scepticism by psychodynamic theorists such as Coodley who noted that:

“One of the newer and important aspects in the treatment of psychosomatic disorders relates to the use of specific hormonal therapy such as corticotrophin (ACTH) and cortisone. It is observed that cortisone and corticotropin are potent pharmacological agents which may deprive the patient of the keystone of his psychological defence. On the other hand, active therapy sometimes led to miraculous results.”

3.2.4 The rise of the medical model

Following the advances in treatment and histology, the perceived importance of psychological mechanisms in Ulcerative Colitis appears to recede from the mid-1950s. (72) highlighted that psychodynamic formulations were open to question and that scientific evidence was not available for them. He noted that “too many factors may contribute to the development of this symptom (diarrhoea) to justify psychological correlations without further analysis of the primary changes in the bowel. When the architecture of the bowel is seriously deranged, or infection has developed within or outside the bowel wall, it is most unlikely that the psychological factors can any longer be clarified by correlative studies of symptoms and psychological events.”

Engel noticed that in many cases rectal bleeding was the first symptom patients experienced and not diarrhoea. The description of a case series which Engel provides, which gives a detailed account of the symptoms, pathology and clinical course, shifts the understanding of colitis away from a psychoanalytic paradigm. (72)

Dick states that handling of psychological difficulties on common-sense lines is sometimes helpful, but formal psychotherapy is seldom indicated, and, importantly, that “the majority have found that A.C.T.H. and cortisone have some effect on this disease.” (73)

In an early trial of cortisone, five of the six patients experienced a dramatic remission. Euphoria, increased appetite, disappearance of fever, and a fall in the erythrocyte sedimentation rate were noticed almost at once. The general conclusion reached at the time was that A.C.T.H. and cortisone influence appetite and produce a feeling of well-being, usually accompanied by a gain in weight. While it was postulated that the production of euphoria is an important factor in the action of A.C.T.H., it was clear that in some cases the physical changes, such as fall in temperature, were so dramatic in their onset and so coincident with the change in mental outlook that it would be difficult to argue that they resulted therefrom. The simpler and more probable explanation was that both resulted from a physical effect of the A.C.T.H., however much the euphoria may later contribute to the patient's recovery by assisting him to face up to and adjust to his difficulties. (73)

The relationship between ulcerative colitis and psychiatric illness became more uncertain and the development of controlled trials and cohort studies added weight to the biomedical model.

A series of 40 patients with schizophrenia and UC compared to 40 with just UC was followed over a period of years to compare the psychological and somatic course of disease, both in duration and severity. There remained a direct correlation between the degree of emotional disturbance and the severity of the colitis. However, a simultaneous increase in psychiatric

and physical symptoms occurred in most cases. (74) This was in direct contrast to the psychoanalytic model of conversion disorder where physical symptoms arose because of unresolved conflict. The authors noted that a simultaneous increase in psychiatric and physical symptoms seemed to be the rule. Furthermore, the study noted that while the interaction of the psychological and physical aspects of ulcerative colitis is frequently discussed in the literature, no assessment had been made of the basic psychiatric diagnosis and its relationship to the course of the disease.

3.2.5 Diagnostic Classification and cohort studies

By the 1960s the psychiatric world had moved from one dominated by psychoanalysis to one dominated by empirical science. The emergence of the randomized controlled trials and controlled cohort studies gave a rational theoretical basis to psychiatric practice. In parallel to this was the introduction of psychiatric classification systems (the International Classification of Diseases or ICD) and operationalized criteria for diagnosis based upon standardized interviews. The discipline of psychology had also broadened beyond Freudian psychology as the sole paradigm. This shifted thinking from descriptions of "inner conflicts" to diagnosable psychiatric illnesses as possible precursors to or sequelae of physical disease. Personality became a dimensional and quantifiable concept and physical illness was correlated to psychiatric disorders such as Major Depressive Disorder or Generalised Anxiety Disorder.

This coincided with the advances in gastroenterology. The diagnosis of Ulcerative Colitis and Crohn's disease no longer simply depended on symptomatic description but a combination of colonic biopsy and histopathology. Blood markers of disease activity, latterly including C reactive protein (CRP), added to this greatly and allowed specific and sensitive measures of diagnosis and severity of disease.

The early observations remained about the possibility that episodes of relapse could be triggered by stress. Studies could then be done which measured a psychiatric disorder objectively followed by objective measurements of bowel disease. Case control and cohort studies began thereby to form a scientific basis for understanding this 'brain-bowel relationship'.

For example, Kurina 2001 used a retrospective case control design, assessing 12,499 patients with IBD to see if episodes of depression or anxiety preceded a relapse of their bowel disease. (75) It was found that both depression and anxiety preceded UC significantly more often than would be predicted from the control population's experience but neither depression nor anxiety occurred excessively before CD. On the other hand, depression and anxiety were significantly more common *after* an episode of CD; whereas UC was followed by anxiety, but not by depression, more often than expected by chance. The results are therefore compatible with the idea that the psychiatric disorders could be aetiological factors in some patients with UC.

Evidence has also emerged for and against the view that life events may be risk factors for IBD relapse. In a prospective study of psychological distress and Crohn's disease activity it was found that levels of depressive symptoms are positively associated with future changes in Crohn's disease activity over a 2 year period (76). In a retrospective case control design, Lebours 2007 showed that occurrence of a Life Event (LE) was more frequent in the 6-month period prior to diagnosis in CD cases than in UC cases or either control group. (77) However, after adjustment for depression and anxiety scores, as well as other characteristics such as smoking status and socio demographic features, this association appeared no longer significant. The authors therefore concluded that Life Events do not appear to be an independent risk factor for IBD onset.

Overall, tthese studies suggest that diagnosable psychiatric disorders, irrespective of their cause, could act as risk factors for disease relapse.

3.2.6 Psychoimmunology

The emerging field of psychoimmunology describes the communication between the nervous and the immune system and increasingly raises important questions about an interaction between psychiatric illness and IBD. Of particular relevance here is the way in which the immune system is apparently suppressed in patients with depressive illnesses. (78)

Major depression is accompanied by immune dysregulation and activation of the inflammatory response system. In a recent meta-analysis of 24 studies of cytokines in depression, patients with major depression had significantly higher concentrations of Tumour Necrosis Factor (TNF) and Interleukin 6 (IL-6) (79). These studies could partially explain the co-occurrence of depression and IBD beyond upset at having an illness.

These interactions have been extended to mice models in which mice are given the depression inducing drug Reserpine. If the colons of these mice are then stimulated with a gastric irritant, the colons of the depressed mice show areas of greater erosion and have more inflammatory cell infiltration. (80) This effect can be reversed by giving the depressed mice an antidepressant. Further, in mice with quiescent colitis, a relapse of inflammation could be induced by an episode of induced depression.

3.2.7 Childhood trauma and adult gut problems

Further interesting work has emerged on the effects of early life experience on the immune system. Disrupted infancy in mice has consequences on adult stress resilience. Mice which had been separated from their mothers in infancy had an exaggerated response to external

stressors as adults as shown by an excessive rise in cortisol. This concept was extrapolated to human subjects where it was shown that women with a history of child abuse had far greater sensitivity to stressors as adults. (81)

Interest has grown in the last 10 years in the consequences of childhood stress on adult physiology. Danese (2009) showed that those who had experienced sexual or physical child abuse had higher levels of C reactive protein (CRP) and white blood cell count. Such work has led to the idea that childhood maltreatment may be a risk factor for inflammatory related illness in adulthood. (82)

Lastly there is increased penetration of bacteria into the colonic of maternally separated mice compared to controls (83). Maternal separation also predisposed rats to develop a more severe immune-driven response to chemically induced colitis (84). Furthermore, maternally separated rats also displayed a higher number of goblet cells and an increase of mucus in the colon than control animals (85). This has implications for susceptibility to infection, as sensitivity to the presence of bacteria in the gut may be increased, which can in turn result in increases in cytokine production

The idea that infant stressors may lead to measurable biological changes in the gut has direct implications for psychiatric illness in inflammatory bowel disease. It therefore follows that childhood experience could also be a risk factor for IBD.

3.2.8 Conclusion

The main objective of this chapter was to collate examples of different paradigms explaining the co-occurrence of psychiatric illness and Inflammatory Bowel Disease.

From the outset both psychoanalytic and bio medical paradigms play an important historical role in describing this association. The main thread of observation, that mental experience can lead to altered bowel habit, appears to ring true through both paradigms. Each paradigm has attempted to give its own explanation for this observation. Both paradigms have attempted to look at the observation in a cross sectional and developmental fashion. Difficulties have existed when attempting to define the mental events: conflicts, stressors, distress, major depressive disorder or generalized anxiety are all terms which have been used to qualify the mental troubles which may precipitate the gastroenterological problem. Psychoanalysis concentrated on childhood development, the influence of which appears to have been ignored during the rise of biological psychiatry only to be revisited as the biological models became more sophisticated.

During this time, Inflammatory Bowel Disease has become associated with objective evidence of measurable pathology in the gut. While approaches to psychiatric illnesses have been influenced by the fall of the psychoanalytical and the rise of the biological model, neither neuroimaging nor genetics have been able to objectify pathology as gastroenterological histology has. Medically unexplained syndromes such as Irritable Bowel Syndrome or Chronic Fatigue Syndrome have yet to be explained biologically. Thus, inflammatory bowel disease provides a fascinating model of multi conceptual influence.

Studies of IBD today include those which suggest that psychotherapy may again be useful in preventing relapses. A historical perspective appears appropriate for IBD as it can highlight how a central theme can be interpreted by different paradigms. The concluding similarity of approach: that childhood can influence the adult gut, should be humbling for both psychoanalysts and biologists alike.

3.3 Inflammatory Bowel Disease and Affective Disorders

The following section will look at existing literature regarding the direct relationship between Inflammatory Bowel Disease and Affective Disorder.

The relationship between psychiatric illness and IBD is a complex one and as discussed, has been discussed at length using many different paradigms since the initial descriptions of both IBD and depression and anxiety.

This section will concentrate on three main areas regarding the relationship between psychiatric illness and IBD.

1. What is the prevalence of psychiatric illness in IBD?
2. Do depression or anxiety affect the prognosis of IBD?
3. What specific aspects of IBD may predict depression or anxiety?

3.3.1 Prevalence of psychiatric illness in IBD

Several studies have sought to describe the prevalence of psychiatric illness, anxiety, stress, psychological distress and quality of life in patients with IBD. The following studies are case control or cross-sectional studies which look at concurrent IBD and psychiatric illness. Below are studies listed when the terms IBD OR Crohn's Disease OR Ulcerative Colitis AND Depression OR Anxiety were entered Medline search in 2009. Studies were excluded if they were not in English, were reviews, were case reports, had lower than 30 subjects or did not quantitatively assess depression or anxiety for patients with IBD. The studies are reported in chronological order in the table below. A systematic review was published in June 2016 on Depression and Anxiety in Inflammatory Bowel Disease and reviewed 171 papers totalling 158,371 participants. Pooled estimate of depression in this group was 15.2% and anxiety was 20.7%. The most used measure was the HADS scale of which the pooled mean score for depression was 5.4 and for anxiety was 7.5 in the disease group. The prevalence in Crohn's disease was higher in than Ulcerative Colitis and higher in active disease compared to remission. Measurement scales included the use of Hospital Anxiety Depression Scale, HADS (37 studies, 7589 participants) Beck Depression Inventory, BDI (17 studies, 761 participants) and Centre for Epidemiological Studies Depression scale CES-D (11 studies, 762 participants). (86)

Paper	Clinical setting	Patient group	Control group	Measure	Main findings
Helzer et al 1982 (86)	Gastroenterology Out patients	50 Crohn's disease patients	50 consecutive out patients with other chronic medical illness	Renard Research Interview	CD patients had significantly higher levels of depression, obsessive compulsive disorder, obsessive symptoms and lifetime psychiatric disorder
Helzer 1984 (87)	Gastroenterology Out patients	50 UC patients	No control group	Renard Research Interview	No significant difference between UC patients and controls.
Andrews et al 1987 (88)	Gastroenterology Out patients	162 IBD out patients	No control group	HADS and DSM-III interview	Prevalence of psychiatric illness in UC and CD was 34% and 33%
Robertson et al 1989(89)	Medical Out patients	80 consecutive IBD out patients	40 out patients with diabetes	HADS	Depression occurring only in patients with active chronic disease.
Tarter et al 1987, (90)	Gastroenterology Out patients	53 consecutive IBD patients	28 normal controls obtained by advertisements		CD patients increased prevalence of anxiety, depression and panic disorder occurring at any time in their life. Panic disorder higher in CD prior to disease onset. UC no increased prevalence of psychiatric disorder before or after disease onset
Drossman et al 1991 (91)	Postal questionnaire	997 members of the Crohn's and Colitis Foundation of America by postal questionnaire	No control group	SCL-90, and the Ways of Coping-Revised.	Crohn's disease had more psychosocial difficulties, which were related to greater symptom severity.
Magni et al 1991 (92)	Gastroenterology out patient	50 consecutive UC patients	50 controls with urolithiasis or symptomatic varicocele.	SAD-L and SCL-90.	Psychiatric disturbance found in 11 UC patients (22%) and 8 controls (16%). at interview a psychiatric disturbance was present in 31 UC patients (62%) and four controls (8%).
Levenstein et al 1994 (93)	Gastroenterology Out patients	79 UC out patients	Patients with and without symptoms of the disease		Symptomatic patients had higher level of perceived stress, trait and state anxiety and depression.
Walker et al 1996 (94)	Gastroenterology Out patients	IBD	Out patients with IBS		65% of patients with IBD had some kind of psychiatric illness compared to 42% of controls.
Addolorato et al 1997 (95)	Gastroenterology Out patients	79 consecutive IBD patients	controls.	STAI, Zung Self-Rating Depression Scale.	rates of the rates of anxiety were as high as 80% for anxiety and 60% for depression during relapse using CD and UC
Guthrie et al 2002 (96)	Gastroenterology Out patients	116 IBD consecutive out patients using		HADS	30 (25.9%) had probable psychological disorder and fifty five patients (47.4%) had possible psychological. No significant differences between CD and UC in depression scores and health-related quality of life.
Nordin et al 2002 (97)	Self-administered Postal questionnaire	492 IBD patients		HADS.	Here, patients with UC reported higher levels in all dimensions of health-related and disease-specific quality of life than did patients with CD. CD patients reported more anxiety and depression than did patients with UC.
Mittermaier et al 2004 (98)	Gastroenterology out patients	60 consecutive out patients IBD patients in remission	no controls	BDI, STAI and PSQ.	At baseline, depression was found in 17 of 60 (28%) patients.
Tanaka et al 2005 (99)	Gastroenterology Out patients	77 UC consecutive out patients	no controls	Perception of difficulties of life, POMS, Jalowiec Coping Scale and the Emotional Support Network Scale	A large number of patients perceived a "decline of vitality or vigor" despite being in the remission phase.
Fuller-Thomson et al 2006, (100)	Population based study	in a Canadian population based study compared IBD patients with	population controls and found that		Prevalence of depressive disorder was 14% over 1 year, three times higher than the general
Lerebours et al 2007 (101)	Gastroenterology Out patients	241 patients with IBD	with 69 patients with Acute Self Limited Colitis (ASLC) and 255 Blood Donors controls.	BATE questionnaire for anxiety and Beck Depression Inventory.	Crohn's disease had significantly higher scores on BDI when compared to ASLC and BD controls. 61% of Crohn's disease patients had BD>4 compared to 38% of blood donor controls and 45% of ASLC. Ulcerative Colitis patients significantly higher BDI scores compared to BD controls but no significant differences with ASLC group. There were no differences on BATE anxiety scores between the UC, ALSC and blood donor groups.
Filipovic et al 2007 (102)	Gastroenterology Out patients	IBD out patients	Patients diagnosed		IBD group had a higher rate of psychiatric illness.

			with Colon Cancer		
Kovacs et al 2007 (103)	Gastroenterology Out patients	IBD,	IBS and healthy controls		
Walker et al 2008 (104)	population-based study of	and 12-month anxiety and mood disorders in subjects with IBD	No controls		found a higher lifetime prevalence of mood disorders (27%) in IBD subjects compared to 12% in the control population.
Hauser et al 2011 (105)	Gastroenterology Out patients	422 IBD patients	140 controls with chronic liver diseases and with 422 age- and sex-matched of the German population.	German version of the HADS	Mental disorders were more frequent in IBD patients with slight (27.7%) and moderate/severe disease activity (49.3%) compared to GP (10.4%) (P < 0.001), but not in IBD patients in remission (11.3%). No difference in levels of anxiety and depression or in the frequency of a probable mental disorder. The levels of anxiety and depression of IBD patients with active disease were higher than that of the GP, but not of the IBD patients in remission. The depression score of the CLD sample was higher than that of the IBD sample (P < 0.001), but not the anxiety score
Barratt et al 2011 (106)	Gastroenterology out patients	453 out patients with IBD,	225 control patients with Coeliac disease and 348 healthy controls.	HADS	HADS scores in the control, celiac, UC and CD groups were: HADS-A =5.3, 7.3, 6.0, 8.0 and HADS-D = 5.5, 7.5, 7.0, 9.0 (both p<0.0001). The HADS A and D were higher in Coeliac than UC patients.

In the 19 studies described above, 14 were samples of diagnosed out patients and 5 were postal questionnaires sent to community patients; 12 studies were controlled, 2 had both medically ill and healthy population controls, 5 had only medically ill control groups and 6 had only healthy controls. Psychiatric illness was found to be higher in 11 of the 13 controlled studies but lower in 2 studies. Psychiatric interviews were used as the method of assessment in only 4 studies. The HADS scale appeared to be the measure most used for this population.

3.3.2 Psychiatric illness and IBD prognosis

It has been reported that the presence of co morbid depression and physical illness may lead to increased symptom reporting, pain, health care usage, surgery, disability, sick leave,

hospital stay and decreased productivity. (107, 108, 109, 110) This relationship may exist across many diseases including Diabetes, coronary heart disease and asthma. While the literature on IBD is slender it is reasonable to presume that this is also the case. In regards to this area there are two important questions. Firstly does co morbid depression exacerbate the disease process and secondly what other healthcare measures may be impaired by co morbid depression.

Two studies noted a clear association between disease activity and levels of symptoms. In 25 UC clinic patients, one study (111) found higher levels of depression and anxiety during an active disease phase, with diminishing symptoms during remission. In a clinical sample of 104 CD and UC patients followed for 6 months, Disease activity paralleled anxiety and depression levels. (112) In a third study, 56 assessed 59 CD and UC patients at 2 time points, reporting similar levels of anxiety and depression at baseline and 12 months later. (113)

There are three prospective studies which provide support for a more direct negative impact of depression on IBD. A 2-year study that assessed CD patients at 2–3-month intervals found that higher depression scores were associated with higher Crohn's Disease Activity Index (CDAI) scores in the subsequent time. (114) A further study assessed 60 IBD patients with clinically inactive disease and assessed them every 3 months for 18 months. Here, Depression level at baseline was significantly correlated with total number of relapses and the median time until first relapse was much shorter for patients with depression (md = 97 days) compared to the group who were not depressed at baseline (md = 362 days; $P < 0.05$). Higher anxiety at baseline was related to more frequent relapses in the follow-up period. (115)

A prospective study of the relationship between depression and treatment response tracked 100 CD clinic patients who were refractory to usual treatments who were given infliximab. (116)

After 9 months until the next flare or the end of the observation period, those with major depressive disorder or higher anxiety symptoms at baseline were
less likely to achieve remission with the infliximab. Multivariate regression analyses confirming depression was an independent determinant of failure to achieve remission in these patients. The presence of a major depressive disorder at baseline was significantly associated with a shorter time to initiating treatment. (116)

With regards to other health measures, Guthrie et al report that co-occurrence of depression or anxiety predicts low health related quality of life in IBD patients. In 222 consecutive patients with IBD, depression was a predictor of increased health care utilization including visits to the gastroenterologist and GP. (117)

3.3.3 What specific aspects of IBD may predict higher likelihood of depression or anxiety?

Many factors can predict depression in a healthy population such as gender, unemployment and age. To date very little literature has focussed on which factors in patients with IBD are likely to predict depressive illness. Three main areas have been highlighted in studies though often they focus on quality of life rather than depressive illness: demographic factors, IBS symptoms and presence of stomas or anastomoses. In terms of demographic factors one

paper suggests that family and peer support is a significant factor leading to fewer psychiatric symptoms in patients with IBD (118).

Many papers look at co morbid IBS like symptoms in IBD. Barratt et al 2011 find that the presence of reflux and IBS like symptoms is associated with reduced QoL and increasing likelihood of anxiety and depression. (107)

Bryant et al report that in 162 patients with IBD, 66% met criteria for at least one Functional Gastrointestinal Disorder (FGID). Those with significant (Hospital Anxiety and Depression Scale ≥ 8) anxiety and/or depression were more likely to meet criteria for coexistent FGID (78% vs 22% and 89% vs 11%, respectively; each $P < 0.001$). It was concluded that Symptoms consistent with FGID correlate with greater psychological comorbidity and poorer HRQoL in a "load-dependent" fashion. (119)

With regards to ileostomy, in 492 Swedish IBD patients, having an ileostomy does not seem to affect patients' quality of life, while having ileoanal anastomosis appears to reduce QoL and affects the HADS score. Having ileoanal anastomosis may lead to more anxiety and depression, while having an ileostomy does not.

In an earlier study the psychiatric morbidity of the 68 subjects seen at 12 months after stoma surgery showed that eleven subjects reported both anxiety and depression at moderate or severe levels and the overall psychiatric morbidity was 15 subjects (22%) This study indicated that a significant minority of patients following stoma surgery have psychological and social morbidity. (120)

3.3.4 Conclusion

The literature on IBD and psychiatric illness suggests several important conclusions. Depression and anxiety disorders are common in IBD ranging from 30-80% during relapses of the condition. However, depression is a common co morbidity in all medical illnesses and sadly only a few studies have included healthy controls or control groups with other medical illnesses in this work. Depression and Anxiety appear to be higher in clinical populations than community samples. The larger studies to address the prevalence have used questionnaires rather than clinical interviews and thus the diagnosis of MDD nor in fact IBD can be totally certain. Despite this depression remains common co morbidity in IBD and is at least as common as in other medial illnesses.

While there has been historical interest on whether psychological symptoms may be precipitants for relapse, there are only a few studies which have been able to answer this question. Life events, perceived stress, diagnoses of anxiety and depression have all been used as the psychological phenotype which could be used as a model. A large prospective study which includes clinical interviews and avoids retrospective bias is lacking. Broadly the literature points towards life events and a depressive episode preceding relapse.

It can also be concluded that both depressive and anxiety symptoms are more common during the active rather than quiescent phase of the illness. This has suggested that psychiatric illness may worsen the prognosis of the illness and the prospective studies do

suggest that likelihood of relapse and time-to-relapse may both be modified by an affective disorder.

In terms of predicting Affective disorders in IBD, the presence of a stoma/pouch appears to increase this likelihood. In other research the presence of IBS like symptoms predicts a worse quality of life in patients with IBD. However, one can question the direction of causality in this relationship.

Lastly the recent use of mouse models of depression in IBD provides an important insight into the co morbidity. One question which can always be levelled at clinical studies is whether IBD symptoms, Depressive disorders and quality of life are being accurately measured or whether propensity to report symptoms in any domain drives the correlations. This weakness in the literature is elegantly combated by mouse modelling which can clearly show a biological relationship between behavioural and intestinal pathology.

The mouse models can be seen as the most convincing evidence that psychiatric factors may well precipitate and worsen colitis and can well explain a high level of comorbidity of affective disorder and IBD

3.4 Coeliac Disease

The following section will outline the main features of Coeliac Disease as patients with Coeliac Disease will be used as a control group for the ISA study.

Coeliac Disease is an inflammatory disorder of the small intestine caused by ingestion of cereal prolamins including gliadins in wheat, hordeins in barley, and secalins in rye. (118) Coeliac disease (CD) affects up to 1% of all individuals in developed countries. (119) Affected individuals experience a gastrointestinal inflammation. Like Inflammatory Bowel Diseases, sufferers suffer from a variety of gastrointestinal symptoms, require adherence to a treatment plan and have the potential of a lifelong autoimmune related illness. Unlike IBD patients, Coeliac Disease may be limited by a regulated diet, there is little place for pharmacotherapy (corticosteroids are generally not prescribed) and patients are unlikely to require hospital admission or surgery. Patients also routinely attend Gastroenterological Outpatient clinics and are often seen by the same physicians treating IBD. The immunological pathways seen in IBD and Coeliac Disease are different. Hence it is these similarities and differences which make Coeliac Disease a choice of comparison group for the ISA study.

3.4.1 Background

The symptoms of Coeliac Disease were first recognized as malabsorbtion and steatorrhoea. Coeliac disease causes variable mucosal inflammation of the small intestine. The characteristic histology is loss of villous height such that, mucosa appears completely flat and there may be subtotal villous atrophy. There is little sex difference. About 10 per cent of first-degree relatives are affected, and twin studies of have shown a concordance of 70 per cent for monozygotic twins.

3.4.2 Clinical features

Coeliac Disease presents at the point that cereals are introduced. Babies show failure to thrive, food refusal and weight loss. Further, clinical features include abdominal distention, muscle wasting, diarrhea with steatorrhoea and vomiting.

In adults, the most common presentations are anemia and abdominal symptoms of discomfort, bloating, flatulence, and an altered bowel habit.

3.4.3 Diagnosis

The gold standard diagnostic test is a small-intestinal biopsy. Serological tests have been developed which include antibodies to gliadin (IgA or IgG isotype), IgA antibodies to reticulin, and IgA antibodies to endomysium. The endomysial antibody is the most useful with a specificity and sensitivity of 90 to 95 per cent.

3.4.4 Clinical Course and Prognosis

Once the diagnosis by a small-intestinal biopsy is known, patients should be started on a Gluten Free Diet (GFD). Nutritional supplements may be necessary if there are low serum concentrations of iron and folate, or biochemical evidence of osteomalacia. After 3 to 4 months, a repeat small-intestinal biopsy is recommended for histological recovery. Dietary compliance may be checked by measuring antiendomysial antibody titre.

The prognosis is excellent if patients adhere to a strict diet. A small group fail to respond to a gluten-free diet. These patients are often not classified as Coeliac but may be referred to as 'non-responsive Coeliac'. Here Corticosteroids with or without Azathioprine has some evidence for treatment.

3.4.5 Coeliac Disease and Affective Disorders

Several studies point to the higher prevalence of Affective Disorders in patients with Coeliac Disease compared to healthy controls. The presence of affective disorders has been described in Coeliac Disease patients since the 1980s. (120, 121)

The prevalence of depression in cross sectional studies of Coeliac patients has been shown to range between 6–57% (122-125) with the lowest prevalence occurring among individuals on a Gluten-Free Diet (GFD). Furthermore, in prospective cohort studies, individuals with Coeliac were at increased risk of subsequent depressive episodes (HR=1.8; 95% CI=1.6–2.2; p<0.001) (126)

Coeliac Disease patients also exhibited high levels of other affective disorders such as dysthymic disorder (8.3%), adjustment disorders (30.5%), and panic disorder (13.9%) The life-time prevalence rate of self-reported depressive symptoms was 39.0% in a study of 883 patients, of whom 270 (11.9%) suffered from current depressive symptoms. (127)

In cross sectional work looking at all gastrointestinal illnesses state anxiety was present in a higher percentage of CD patients with respect to controls, while trait anxiety was not significantly different indicating that anxiety could be related to the physical symptoms present. (128)

Depressive symptoms do not appear to be influenced by age, age at the time of diagnosis, gender, socioeconomic variables, Gluten Free Diet (GFD) duration and GFD referred compliance, which suggests that depressive symptoms may be considered a common feature of Coeliac.(129) Furthermore anxiety disorder in Coeliac patients was related to a sense of being different from the ordinary population and, particularly in women, to a low level of general well-being. (129)

Roos et al. found no increased risk of depressed mood in treated Coeliac Disease when there was objective evidence of remission (return of villous structure at repeat biopsy or absence of IgA endomysial/gliadin autoantibodies) after the institution of GFD. Coeliac patients evaluated before and after 12 months of GFD were shown to have an improvement of state anxiety. (130)

In studies on Quality of Life (QoL), Coeliac Disease patients demonstrated lower QoL than controls and this was mediated by physical symptoms and depression.[19, 20] Other factors cited as leading to poor QoL include an unsatisfactory sex life and difficulty in adapting to the chronic nature of Coeliac Disease (121,122)

3.4.6 Aetiology of Comorbidity

Several factors have been hypothesized to explain the high prevalence of Affective Disorders in Coeliac Disease patients. Reduced cerebral monoamine production is consistently implicated in affective disorder. One study showed a significant reduction of serotonin metabolites in cerebral spinal fluid of Coeliac Disease patients. (131) Further work showed an improvement in mood after GFD and a subsequent elevation in plasma concentrations of tryptophan. (132)

Folate and homocysteine may play important roles in the pathogenesis of depression. It is possible that due to malabsorbtion these will be lower in patients with active Coeliac Disease and could lead to low mood. (133, 134)

3.4.7 Treatment of Comorbidity

In one study an improvement of state anxiety was found after GFD, while depression was still present and was related to the limitation of GFD in daily life. While a reduction of anxiety disorders after GFD could be related to the improvement of physical symptoms, it is thought that depression is sustained by the reduction in the quality of life (QoL). This may

be due in part to the decreased sense of well-being, and in part to dietary restrictions that lead to difficulties in daily social relationships. (135)

One trialled psychological support for Coeliac Disease patients and showed that in those with affective disorders, psychological support can reduce depression and increase GFD compliance. (136)
Importantly, treatment of co morbid psychological difficulties can lead to improved dietary compliance in this group. (137)

3.4.8 Conclusion

Patients with Coeliac disease experience a dietary related autoimmune activation leading to several gastrointestinal symptoms. They appear to experience a higher level of affective disorder symptoms than the general population, yet the affective symptoms reduce when patients are treated. The use of Coeliac disease as a control group will be to evaluate whether IBD patients have a significantly higher level of affective disorder. If so it may be possible to suggest that this higher rate could be due to the differences from coeliac disease. Importantly it will be interesting to see whether coeliac patients have a similar sociodemographic profile as IBD patients as this will allow sociodemographic factors to be controlled for as predictors of affective illness.

Below is a table summarising similarities and differences between IBD and Coeliac disease for the purposes of the ISA study.

	Inflammatory Bowel Disease	**Coeliac Disease**
Socio demographic profile	Social class I-V Male: Female ratio 1:1	Social class I-V Male: Female ratio 1:1
Symptoms	Diarrhea, bowel frequency, urgency, abdominal pain	Diarrhea, bowel frequency, urgency, abdominal pain
Age of Onset	Child or young adult	Child or young adult
Diagnosis and investigations	Diagnostic biopsy, regular serology, serum inflammatory markers, radiology	One diagnostic biopsy, infrequent serology if complications
Diet	Evidence that dietary factors may improve course	Strict diet as main therapeutic measure
Treatment	Several pharmacotherapy's, many with significant side effects	In general, no pharmacotherapy
Corticosteroids	Used as mainstay of treatment	Used rarely in treatment resistance
Health service usage	Frequent outpatient appointments, hospital admissions	Rare outpatient appointments, admission generally unlikely
Inflammation	Known immunological pathways including crp, interleukins, tnf	IgA serology
Complications/comorbid conditions	Uveitis, Arthritis, Renal Caliculi, Infertility, Bowel Cancer, Iritis	Thyroiditis, Addison's disease, Fibrosing alveolitis, systemic lupus erythematosus, and polyarteritis, Lymphoma
Treatment Complications	Stoma, Cushings Disease	No major complications
Prognosis	Probably lifelong relapsing remitting illness	Remission if diet maintained
Mortality	Increased mortality associated with complications, treatment	No change in mortality

4.0 Affective Disorders

The following chapter will focus on Affective Disorders, how they relate to chronic medical illness and their relationship to immunology.

4.1 Clinical features and management of affective disorders

This thesis will focus on three main diagnoses of Affective Disorder: Depression, Bipolar Disorder and Anxiety Disorders. The Anxiety disorders relevant to this thesis are Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD), Simple Phobia and Panic Disorder.

4.1.1 Depression

Depression is a major cause of morbidity worldwide with lifetime prevalence up to 17%. (141) It affects 298 million people worldwide (4.3% of global population) and is the leading cause of disability as measured by Years Lived with Disability (YLDs). (142) Diagnosis of Depression is defined by the ICD-10 as outlined in the box below

The box below outlines the ICD-10 diagnostic criteria

F32 Depressive episode	The depressive episode should last for at least 2 weeks. There have been no hypomanic or manic symptoms sufficient to meet the criteria for hypomanic or manic episode The episode is not attributable to psychoactive substance use
F32.0 Mild depressive episode	A. The general criteria for depressive episode (F32) must be met. B. At least two of the following three symptoms must be present: (1) Depressed mood to a degree that is definitely abnormal for the individual (2) loss of interest or pleasure in activities that are normally pleasurable; (3) decreased energy or increased fatigability. C. An additional symptom or symptoms from the following list should be present, to give a total of at least four: (1) loss of confidence and self-esteem; (2) unreasonable feelings of self-reproach or excessive and inappropriate guilt; (3) recurrent thoughts of death or suicide, or any suicidal behaviour; (4) complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation; (5) change in psychomotor activity, with agitation or retardation (either subjective or objective); (6) sleep disturbance of any type; (7) change in appetite (decrease or increase) with corresponding weight change). (8) Marked loss of libido.
F32.1 Moderate depressive episode	A. The general criteria for depressive episode (F32) must be met. B. At least two of the three symptoms listed for F32.0, criterion B, must be present. C. Additional symptoms from F32.0, criterion C, must be present, to give a total of at least six.
F32.2 Severe depressive episode	All three of the typical symptoms noted for mild and moderate depressive episodes (F32.0, F32.1) should be present, plus at least four other symptoms, some of which should be of severe intensity.

In the UK, around 3.4% of people with major depression commit suicide and up to 60% of people who commit suicide had depression or another mood disorder. (143)

In addition to psychological features, patients with depression often experience physical symptoms including increased physical pain and fatigue. One or more pain symptoms are present in 65% of depressed patients, and anywhere from 5 to 85% of patients with pain will be suffering from depression, depending on the context. The diagnosis of depression is often delayed or missed, which leads to worse prognosis. (144)

Onset is most commonly between the ages of 30 and 40, and there is a second, peak of incidence between ages 50 and 60. (145) Fifty-one percent of those with major depression also suffer from lifetime anxiety. It has been suggested that up to 80% of those suffering from their first major depressive episode will suffer from at least 1 more during their life, with a lifetime average of 4 episodes. (146)

Depression in a medically ill population is complicated as fatigue, appetite disturbance and sleep disturbance may be caused by the physical illness rather than depression. (147)

4.1.1.2 Aetiology of depression

The aetiology of depression is best understood by a biopsychosocial model. Biological factors include a heritability estimate of 40% and a number of candidate genes implicated including polymorphisms in the 5HTT and BDNF genes. (148) Neuroimaging changes have been consistently noted in the anterior cingulate, hippocampus and amygdala (149, 150)

Lack of neurogenesis in the hippocampus has been more recently implicated (151) Here hippocampal neuronal loss correlates with impaired memory and dysthymic mood and Antidepressants which stimulate neurogenesis can increase hippocampal volume. (151)

Multiple social factors have been shown to predict depressive illness. In women, lack of a confiding relationship, responsibility for the care of several young children at home, and unemployment can increase the risk of depression. (152) In older adults, health problems, the death of a significant other, or a change in social relationships because of their own health-related life changes have been cited as factors. (153) Depression is often associated with unemployment, poverty and stressful life events (154, 155)

4.1.1.3 Management of depression

The NICE guidelines on management of depression in adults suggest a stepwise model of treatment. Of relevance to this thesis there exists specific guidance in relation to those with concurrent physical illnesses and depression. (156) See text box

NICE Guidelines for people with Depression and a chronic physical health problem

For patients with persistent sub threshold depressive symptoms or mild to moderate depression and a chronic physical health problem, and for patients with sub threshold depressive symptoms that complicate the care of the chronic physical health problem, consider offering one or more of the following interventions, guided by the patient's preference:

- a structured group physical activity programme
- a group-based peer support (self-help) programme
- individual guided self-help based on the principles of cognitive behavioural therapy (CBT)
- computerised cognitive behavioural therapy (CCBT)[1]

Do not use antidepressants routinely to treat sub threshold depressive symptoms or mild depression, but consider them for people with:

- mild depression that complicates the care of the physical health problem or
- a past history of moderate or severe depression
- initial presentation of sub threshold depressive symptoms present for at least 2 years
- sub threshold depressive symptoms or mild depression persisting after other interventions

For patients with initial presentation of moderate depression and a chronic physical health problem, offer the following choice of high-intensity psychological interventions:

- group-based CBT
- individual CBT for patients who decline group-based CBT or for whom it is not appropriate, or where a group is not available
- behavioural couples therapy for people who have a regular partner and where the relationship may contribute to the development or maintenance of depression, or where involving the partner is considered to be of potential therapeutic benefit.

When an antidepressant is to be prescribed for a patient with depression and a chronic physical health problem, take into account the following:

- the presence of additional physical health disorders
- the side effects of antidepressants, which may impact on the underlying physical disease (in particular, SSRIs may result in or exacerbate hyponatraemia, especially in older people)
- that there is no evidence as yet supporting the use of specific antidepressants for patients with particular chronic physical health problems
- interactions with other medications

Consider collaborative care for patients with moderate to severe depression and a chronic physical health problem with associated functional impairment whose depression has not responded to initial high-intensity psychological interventions, pharmacological treatment or a combination of psychological and pharmacological interventions

4.1.2 Bipolar disorder

Bipolar disorder is a severe lifelong psychiatric illness characterized by episodes of both low and high mood. Its importance in this thesis relates to whether bipolar disorder may be seen more commonly in patients with Inflammatory Bowel Disease and whether patients receiving corticosteroid medication are more likely demonstrate a bipolar mood disorder episode. The relationship between corticosteroid medication and mood disorder has already been described in chapter 2. There is little evidence that Bipolar Disorder is likely to be more common in chronic medical conditions. National Epidemiological Catchment Area survey suggested that 0.8% of the population experience a manic episode at least once and a further 0.5% have a hypomanic episode. (157,158)

The incidence of bipolar disorder is similar in men and women. Bipolar illness has higher heritability estimates than unipolar depression (up to 80%).

To gain a diagnosis of bipolar illness, patients must experience a hypomanic or manic episode. The clinical features of these can be found in text box below.

F30.0 Hypomania	A. The mood is elevated or irritable to a degree that is definitely abnormal for the individual concerned and sustained for at least four consecutive days. B. At least three of the following must be present, leading to some interference with personal functioning in daily living: (1) increased activity or physical restlessness; (2) increased talkativeness; (3) difficulty in concentration or distractibility; (4) decreased need for sleep; (5) increased sexual energy; (6) mild spending sprees, or other types of reckless or irresponsible behaviour; (7) increased sociability or over-familiarity. C. The episode does not meet the criteria for mania (F30.1 and F30.2), bipolar affective disorder (F31.-), depressive episode (F32.-), cyclothymia (F34.0) or anorexia nervosa (F50.0). D. Most commonly used exclusion criteria: the episode is not attributable to psychoactive substance use (F1) or any organic mental disorder, in the sense of F0.
F30.2 Mania	A mood which is predominantly elevated, expansive or irritable and definitely abnormal for the individual concerned. This mood change must be prominent and sustained for at least a week (unless it is severe enough to require hospital admission) B. At least three of the main symptoms must be present (four if the mood is merely irritable), leading to severe interference with personal functioning in daily living: C. The absence of hallucinations or delusions, although perceptual disorders may occur (e.g. subjective hyperacusis, appreciation of colours as specially vivid, etc.).D.

For research purposes symptom scales have been used which include the Young Mania Rating Scale and the Altman self-rating mania scale. The usage of these will be discussed further in the methodology section.

4.1.3 Anxiety Disorders

Anxiety is noted to co-exist in 50% of cases of Depression and can be sometimes seen as part of the phenotypic continuum of depressive illness. A significant component of research on depression in medical illness includes anxiety dimensions. Anxiety symptoms have been shown to have specific clinical implications in medical illness. Anxiety Disorders have emotional, cognitive and somatic symptoms. The cardinal somatic symptoms of Anxiety

include tachycardia, dry mouth, dyspnoea or tachypnoea, urinary urgency, rash, tremor. Cognitive symptoms include fear of dying, need to escape and worry.

In this thesis, Anxiety will be defined as both categorical diagnosis and dimensional levels of anxiety. Four categorical diagnoses will be briefly outlined below: Generalized Anxiety Disorder, Panic Disorder, Simple Phobia and Obsessive-Compulsive Disorder.

Somatic Symptoms of Anxiety	(1) Palpitations or pounding heart, or accelerated heart rate. (2) Sweating. (3) Trembling or shaking. (4) Dry mouth (not due to medication or dehydration). Symptoms concerning chest and abdomen (5) Difficulty breathing. (6) Feeling of choking. (7) Chest pain or discomfort. (8) Nausea or abdominal distress (e.g. churning in stomach). Symptoms concerning brain and mind (9) Feeling dizzy, unsteady, faint or light-headed. (10) Feelings that objects are unreal (derealization), or that one's self is distant or "not really here" (depersonalization). (11) Fear of losing control, going crazy, or passing out. (12) Fear of dying (13) Hot flushes or cold chills. (14) Numbness or tingling sensations. (15) Muscle tension or aches and pains. (16) Restlessness and inability to relax. (17) Feeling keyed up, or on edge, or of mental tension. (18) A sensation of a lump in the throat, or difficulty with swallowing.
Generalized Anxiety Disorder	A. A period of at least six months with prominent tension, worry and feelings of apprehension, about every-day events and problems. B. At least four symptoms out of the above list of items must be present, of which at least one from items (1) to (4)
F40.2 Specific (isolated) phobias	A. Either (1) or (2): (1) marked fear of a specific object or situation not included in agoraphobia (F40.0) or social phobia (F40.1); (2) marked avoidance of such objects or situations. Among the most common objects or situations are animals, birds, insects, heights, thunder, flying, small enclosed spaces, sight of blood or injury, injections, dentists and hospitals Symptoms of anxiety in the feared situation at some time since the onset of the disorder, as defined in criterion B for F40.0 (Agoraphobia). C. Significant emotional distress due to the symptoms or the avoidance, and a recognition that these are excessive or unreasonable. D. Symptoms are restricted to the feared situation, or when thinking about it.
Panic Disorder **F41.0 Panic disorder [episodic paroxysmal anxiety]**	A. Recurrent panic attacks, that are not consistently associated with a specific situation or object, and often occurring spontaneously (i.e. the episodes are unpredictable). The panic attacks are not associated with marked exertion or with exposure to dangerous or life-threatening situations. B. A panic attack is characterized by all of the following: (a) it is a discrete episode of intense fear or discomfort; (b) it starts abruptly; (c) it reaches a crescendo within a few minutes and lasts at least some minutes; (d) at least four symptoms must be present from the list above, one of which must be from items (1) to (4):
F42 Obsessive Compulsive disorder	A. Either obsessions or compulsions (or both), present on most days for a period of at least two weeks. B. Obsessions (thoughts, ideas or images) and compulsions (acts) share the following features, all of which must be present: (1) They are acknowledged as originating in the mind of the patient, and are not imposed by outside persons or influences.

	(2) They are repetitive and unpleasant, and at least one obsession or compulsion must be present that is acknowledged as excessive or unreasonable. (3) The subject tries to resist them (but if very long-standing, resistance to some obsessions or compulsions may be minimal). At least one obsession or compulsion must be present which is unsuccessfully resisted. (4) Carrying out the obsessive thought or compulsive act is not in itself pleasurable. (This should be distinguished from the temporary relief of tension or anxiety). C. The obsessions or compulsions cause distress or interfere with the subject's social or individual functioning, usually by wasting time. D. Most commonly used exclusion criteria: not due to other mental disorders, such as schizophrenia and related disorders (F2), or mood [affective] disorders (F3).

4.2.0 Depression in medical illness

There exists extensive literature about depression in medical illness, a significant amount of which could relate to, but is not covered by the work on depression in IBD. There are three central themes which will be discussed here. Firstly, what is the epidemiology of affective disorder in a medically ill population? Secondly what is the relationship between physical and mental illness? Thirdly, what are the consequences of a co morbid affective disorder?

4.2.1 Epidemiology

With a globally ageing population, individuals are increasingly likely to spend more of their lifetime with a chronic illness associated with age and those with a chronic medical condition are likely to live longer. Due in part to co morbid medical illness, when moving from the community to primary-care, to inpatient medical settings, the prevalence of major depression increases from 3%–5% to 5%–10% to 10%–14% (159-162)

In earlier epidemiological work in the USA, in the Epidemiologic Catchment Area Study found that people suffering from one of eight medical disorders had a 41% increase in the risk of having any recent psychiatric disorder (anxiety, affective, substance abuse disorders) compared with people without chronic medical disorders. (163)

In a further US study there was a 4% risk of developing major depression with any long-term medical condition compared with 2.8% of those without medical conditions. (164)

With regards to case-controlled studies in specific illnesses the odds of major depression in diabetes patients was twice that of a non-diabetic group (165) and when using structured psychiatric interviews, 11%–15% of diabetics were found to meet criteria for major depressive disorder (165)

In an international epidemiological study carried out by the WHO in 60 countries, including subjects from Europe, Asia, Africa and the Americas the point prevalence of Depression alone stood at 3·2% (3·0–3·5) when using the Composite International Diagnostic Interview. (9) In those who had several co morbid chronic medical illnesses the rates of depression were higher. For patients with diabetes, at a worldwide level, 9·3% (7·3–11·3), 10·7% (9·1–12·3) with arthritis, 15·0% (12·9–17·2) with angina, and respondents with asthma at 18·1% (15·9–20·3). (166)

For the 7·1% (6·6–7·6) of subjects who had two or more chronic physical conditions, nearly a quarter (23%) also had depression in addition to their existing medical illnesses. The study

concluded that the prevalence of depression in respondents with chronic diseases is significantly higher than in respondents without chronic diseases (3·2%, p<0·0001). (166)

Less literature is available for a Scottish population but in a study of out patients with cancer and depression one quarter of the cancer outpatients 674 out of 3071 (22%; 95% confidence interval (CI) 20–23%) met criteria for clinically significant emotional distress (total HADS score 15 or more). A diagnosis of depression as made by telephone SCID was made in 13% of this population. (167)

4.2.2 Why does depression co-exist with physical illness?

Katon states five postulates for why depression may occur in physical illness. (168) These are:

1) Depression is a risk factor for the development of some specific diseases
2) Depression is a secondary psychological reaction to the development of the disease
3) Depression is secondary to the complications or aversive symptoms of that disease
4) Depression is secondary to the side effects from medication used to treat these
5) The chronic medical illness has a direct pathophysiologic effect on the brain or has indirect physiologic effects (such as via cytokines)

A sixth point which has not been raised by Katon is that sociodemographic factors may be confounders for both the physical and mental illness.

4.2.3. What are the consequences of comorbid affective disorder?

In considering the relationship between affective disorder and inflammatory bowel diseases, the consequences of comorbidity are important. Comorbidity will be looked at in terms of adverse health behaviours, social role change, symptom reporting and health service usage.

Patients with depression may exhibit poorer self-care or hygiene, have unhealthier diets or may do less exercise. All these simple behaviours may understandably lead to poorer physical health. Anxiety and depression are associated with poor adherence to self-care regimens (diet, exercise, cessation of smoking, medication regimens) and increased medical complications in patients with chronic medical illness, which should lead to increased symptom burden (29, 30) Studies have reported that patients with major depression have higher rates of adverse health-risk behaviours, such as sedentary lifestyle, smoking, and over-eating. These may lead to a higher incidence of diabetes and heart disease (170) Subjects with major depression were shown in the Epidemiologic Catchment Area Study to have a significantly higher rate of smoking compared with non-depressed respondents (165)

With regards to social functioning, data from the Medical Outcomes Study showed that patients with major depression perceived their vocational and social functioning and general health to be more impaired than patients with one of seven other medical conditions (171). When major depression was co morbid with chronic medical illness, there was additive functional impairment (171). Longitudinal studies have shown that affective

disorders are more predictive of functional impairment over time than severity of physical illness. For example, Sullivan and colleagues demonstrated that symptoms of affective disorder at initial diagnosis of coronary disease by angiogram were more highly correlated with functional impairment at both 1- and 5-year follow ups than was any physiologic measure (172)

Data from both mixed-aged and elderly samples of primary-care patients have found significantly higher medical costs in patients with either depressive symptoms or major depression compared with patients without depression.
The increase in costs is a consequence of increased primary care visits, specialty visits, mental health visits, emergency room visits, pharmacy costs, laboratory and x-ray examinations, and inpatient costs. (167) It has also been noted that there is an Increase in length of hospital stay (173) in patients with both benign and malignant illness in those with co morbid depression compared with those without depression. (174)

After adjusting for sociodemographic characteristics, alcohol dependence and chronic physical illness burden, the presence of co-morbid depression was associated with significantly greater (approximately double the) likelihood of health-care utilization and increased functional disability and work absence compared to the presence of a chronic physical illness without co-morbid depression. The impact of depression was seen across many illnesses with the strongest associations seen for work absence. Depression was associated with a significantly higher probability of health-care utilization in the previous 12 months (174)

Patients with co morbid depression were seen to report more physical symptoms. There appears to be an amplification of chronic disease symptoms in patients with chronic medical illness who have comorbid anxiety or depressive disorders. (175)

Furthermore, patients with chronic medical illness and comorbid depression or anxiety compared to those with chronic medical illness alone reported significantly higher numbers of medical symptoms when controlling for severity of disease. (175)

A systematic review looking at associations between depression and mortality found 44 studies (72%) reporting a positive association and 17 (28%) reporting no association. Here positive studies had a longer median length of follow-up and were more likely to use structured psychiatric interviews to define major depression rather than depression self-rating scales. (176)

The co-occurrence of affective disorder and physical illness has been studied across many physical illnesses. It can be concluded that depression is common in physical illness and is associated with many social and medical complications such as role impairment and disease severity. The relationship may itself be bidirectional as psychiatric symptoms as seen above may be a cause and consequence of these complications. The inclusion of this section in the thesis serves to form a basis for several hypotheses which are not covered in the IBD literature.

4.3.0 Psychoimmunology: Depression and Immunological Function

The relationship between chronic medical illness is and affective disorder, prime facie, a simple one. Patients suffering from chronic pain, disability, loss of role, difficulties in relationships and loss of employment are understandable reasons for onset of a depressive illness. One of the central themes of this thesis, however, is that depressive illness in the context of chronic medical illness can be understood through a biological paradigm. The immunological changes seen in medical illnesses may themselves lead to depressive symptoms. This section will concentrate on immunological seen in depression as it is these changes are seen in both the pathophysiology and treatment of Inflammatory Bowel Disease.

4.3.1 Cytokines in Depression

A significant literature suggests that depressive illness is accompanied by immune dysregulation. Activation of the inflammatory response system has been demonstrated by increased production of Pro inflammatory cytokines such as interleukin IL-1, IL-2, IL-6, interferon (IFN), tumor necrosis factor (TNF), the soluble IL-6 receptor (IL-6R), and the IL-1 receptor antagonist (IL-1RA) (177-186).

Proinflammatory cytokines may cause the development of depressive symptoms (187). Furthermore, evidence in the context of chronic inflammatory disease demonstrates that an improvement of mood and cognitive symptoms can be seen with anti-inflammatory treatment. Cytokines have been shown to induce neuroendocrine and central

neurotransmitter changes like those in depression (187), and it has been demonstrated that treatment with IFN-gamma can precipitate depression (188).

However, the association between cytokines and depression is not consistently significant in all studies or for all cytokines (188, 189, 190)

In studies of TNF alpha measurements were made in 438 depressed and 350 non-depressed subjects extracted from 13 studies. The meta-analysis noted that there were significantly higher concentrations of TNF-alpha in depressed subjects compared with control subjects. (191)

In studies of IL-6, measurements were made in 492 depressed and 400 non-depressed subjects extracted from 16 studies. Depressed patients had significantly higher concentrations of IL-6. (192) In four studies of IFN-gamma, for 131 depressed and 107 nondepressed subjects. Concentrations of IFN-gamma did not differ between groups.

IL-6 and TNF-alpha are thought to either decrease levels of serotonin in the brain or activate the HPA axis (193, 194). Other studies found that pro-inflammatory cytokines activate serotonin degrading enzymes (195). There have be many articles published which report a decrease in depressive symptoms in patients receiving Infliximab (IFX), a monoclonal antibody against TNF-alpha, which antagonises the effects of TNF-alpha. In 2009, Soczynska et al. (196) reviewed the effect of anti-TNF-alpha drugs on depressive symptoms related to bipolar disorder in patients suffering from autoimmune diseases and advanced cancer. This literature review looked at six papers which studied the effect of TNF-alpha antagonists

Adalimumab, Etanercept and Infliximab on the depressive symptoms. The authors suggest that infliximab as well as other TNF-alpha antagonists may be therapeutic for somatic, cognitive and affective symptoms associated with the depressive symptoms. However, it remains unclear whether infliximab is having a direct therapeutic effect on depressive symptoms or whether it act indirectly through relieving the autoimmune symptoms.

Results from a 2-year, randomized, comparator-controlled trial evaluating anti TNF therapy with in patients with rheumatoid arthritis reported significant improvements in quality of life and somatic symptom measures (197)

In one randomized, double-blind, placebo-controlled trial of patients with psoriasis (198) subjects receiving Etanercept had a 47% reduction in psoriatic measures and at least a 50% improvement in HAMD and BDI at 12 weeks. However, significant improvement in depressive symptoms was less correlated with objective measures of skin clearance or joint pain (198).

Two studies looked specifically at the change in affective symptoms in patients with Crohn's disease treated with Infliximab. Persoons et al. reported that the prevalence of depressive disorder at baseline predicted significantly lower remission rates (29% vs. 70%) at 4 weeks as compared to subjects without depression. A significant decrease in time to retreatment was also reported for subjects with depression. A significantly smaller proportion of subjects met criteria for depression at 4 weeks (16% vs. 24%) as compared to baseline (199)

Minderhoud et al. in a single blinded study enrolled patients with Crohn's disease (n = 14), each of whom received placebo at baseline, followed by infliximab at 2 weeks. (200) A significant effect of Infliximab was observed on the Centre of Epidemiological Studies Depression scale (CES-D) at 4 weeks, which was not seen in the placebo group. (200)

This evidence concludes that, the results of these studies provide support that TNF-a antagonists may offer therapeutic benefit for somatic, cognitive, and affective symptoms associated with mood disorders.

4.3.2 C-Reactive Protein

C-reactive protein (CRP) is an acute-phase protein which is a member of the class of acute-phase reactants, as its levels rise dramatically during inflammatory processes and this is due to a rise in the plasma concentration of IL-6. CRP rises to 50,000-fold in acute inflammation, such as infection. It rises above normal limits within 6 hours, and peaks at 48 hours. Emerging literature has supported the notion that CRP is elevated in depression. Results from a prospective cohort study demonstrated significant interaction between C-reactive protein and depression, such that moderately increased C-reactive protein in depressed men was predictive of a subsequent first coronary event (201) When men were assessed 2 months after acute coronary syndrome, it was found that depression and C-reactive protein were overlapping prognostic risks.

Other studies showed that current depression diagnosis alone is less likely to be related to inflammation risk as measured by HS CRP, but current depression and maltreatment history

combined seem to be good predictors of inflammation levels. Moreover, even in the absence of a current diagnosis of depression, maltreatment history alone still confers increased risk of clinically relevant inflammation levels. (202)

5.0 Methodology

The following section on methodology will outline patient population, measurement scales, statistical methods and ethical approval

5.1 Patient population

Of many studies on the prevalence of psychiatric and psychological comorbidities in Inflammatory Bowel Disease, many different clinical populations have been used as can be seen in Chapter 3. From the literature these can be divided into two main groups. However, both main populations used come with important selection and observer biases.

Firstly, there are large population cohorts who have been recruited via postal surveys or patient membership organisations. This methodology carries the advantage of increased study power allowing assessment of multiple clinical variables. However, there are three principle drawbacks. As many of these studies have been conducted on patients who are members of patient organisations, their histological diagnosis cannot be confirmed. It is possible that some of this group may carry a diagnosis of IBS rather than IBD. Secondly a major weakness in postal surveys is that failure to get good phenotypic psychiatric assessment. There exists an inherent methodological weakness in self-report of psychiatric symptoms which may be unconfirmed by clinical assessment, GP records or record of medication. A third drawback in these studies is response bias. At best 60% of the

populations have responded and are either more likely to be those who have lower rates of psychiatric illness or those who have possible higher levels of health anxiety. (see chapter 3)

The second type of study population is drawn from in-patient and out-patient clinical populations. A disadvantage of this group relates to the opportunity to power the studies as well. Rarely do these studies exceed a few hundred subjects. It is possible that patients with co morbid psychiatric illness may be either more or less likely to access health services. Furthermore, the out-patient and in-patient population are likely to be those with more severe disease. (see chapter 3)

The main objective of this thesis is to determine which inflammatory, disease, treatment and socio demographic factors predict affective disorder in IBD. It is therefore a prerequisite that subjects have a histological diagnosis of IBD, that it is sufficiently powered to measure predictors but also that potential predictors exist in the study population i.e. to assess the impact of corticosteroid medication as a risk factor, many patients taking this medication will be required. It is possible that a community sample may not have sufficiently severe disease to study treatment or disease variables. A further advantage of clinical compared to community samples will be the opportunity to perform more extensive psychiatric phenotyping.

A secondary question will be to address the prevalence of affective disorder in clinical populations. Even if clinical populations are unrepresentative of IBD patients, this group are having direct contact with gastroenterologists and thus there is the potential to shape

services around this population. The ISA study population is therefore taken from outpatient gastroenterology clinics over a set time frame.

5.2 Site

The city of Edinburgh and surrounding area has an approximate population of 468,000 as of 2010. The city includes both affluent and deprived areas but has less ethnic diversity compared to other UK cities. Socio demographically Edinburgh may be unrepresentative of all UK cities due to a large affluent population centred on the universities and financial sector institutions.

The city hosts two University teaching hospitals, the Western General Hospital and The Royal Infirmary of Edinburgh. With an approximate lifetime prevalence of 1/250, it can be estimated that there are around 1900 IBD patients in the city.

Regarding service configuration in Edinburgh, all IBD patients attend the Department of Gastroenterology outpatient clinic at the Western General Hospital. Some patients requiring complex surgery or other medical and surgical co morbidity additionally attend the Royal Infirmary of Edinburgh. The importance of this service configuration is that all patients with a histological diagnosis of IBD are likely to be known to one clinical site and attend one primary clinic for treatment.

5.3 Cohort

Patients with Inflammatory Bowel Disease were recruited into prospective cohort and genetic studies in Edinburgh from 1995. Patients were recruited from in patient and out patient populations and their clinical phenotype; treatment and genotype were followed over the subsequent 20 years. Existing data includes disease extent, severity, surgery, socio demographic variables, smoking and treatment. Methodology from these studies is documented elsewhere. (203)

Ulcerative Colitis phenotype at baseline was classified by disease extent, disease severity, and need for surgery. The extent of disease has been documented at the time of latest follow-up. (203) Disease extent has been defined as disease extending beyond the splenic flexure, left-sided colitis as disease extending to the splenic flexure, and proctitis as disease limited to the rectum as determined by histologic and macroscopic evidence. Other phenotypic details such as smoking, family history, presence of primary sclerosing cholangitis, and other extra intestinal manifestations were also recorded.

Crohn's Disease patients were described according to the Vienna Classifications. Previous work has shown that disease behaviour is consistent over time and therefore disease behaviour was analysed only at time of diagnosis and at latest follow-up. (203)
In one study previously published by the gastroenterology group, two hundred thirty-one patients with well-characterized CD were categorized according to the Vienna classification and were further assessed at 5-, 10-, 15-, and 20-year stages.

In this study additional clinical and biologic parameter that may relate to the progression of disease type had been also collected which comprised gender, smoking history, family history of IBD, surgical history, the presence of joint problems, azathioprine use, ASCA status, and NOD2/CARD15 status. Their median length of follow-up was 138 months. (203)

The data from other studies on the same cohort shows that the behaviour of disease predicts location of disease and ASCA status significantly but shows no difference with regards to age and gender of patient, smoking status or family history. (204)

After 5 years, disease behaviour, in this cohort, continues to significantly predict disease location. Furthermore, there is a significant relationship between disease behaviour and gender. (204)

Disease behaviour at 10 years shows that there continues to be a relationship between disease behaviour and location. However, the relationship with gender disappears. (204)

The importance of this data for the ISA study is that, in looking for predictors of affective illness in this population, both disease behaviour and disease location may be predictors. If subsets of disease behaviour are predictors of subsequent affective illness, this could allow targeted screening of IBD phenotypes for psychiatric illness. The relationship between disease behaviour or location may impact on affective illness through several mechanisms which would include disease behaviour relating to a more severe subtype of disease,

symptom experience or causal mechanism (e.g. could certain disease subtypes have related to smoking, poor diet or family history – each of which may be separately related to an affective illness).

5.4 Cross Sectional Study Assessment

Data was collected from the subjects as part of the cross-sectional part of the study as shown in the table below.

Medical Diagnosis and Physical Symptoms	Psychiatric Phenotype	Demographic Background	Medication	Inflammatory Biomarker
Colitis Activity Index (UC)	HADS	Gender	Which Medication	CRP
Harvey Bradshaw Index (Crohn's disease activity)	Altman Self Rated Mania	Employment	Present/Past	ESR
Surgery	Past Psychiatric History	Incapacity Benefits	Corticoteroid Dose/Duration	Calprotectin
Stoma		Marital Status	Immuno-modulators	WCC
Admissions		Smoking	Adherence (MARS)	HBC
Episodes		Alcohol		

5.5 Medical Diagnosis and Physical Symptom Scales

Diagnosis of Crohn’s Disease and Ulcerative colitis was made based on histological samples and all subjects in the ISA study had a confirmed diagnosis of IBD.

Patients with Crohn's Disease had symptoms measured by the Harvey Bradshaw Index which is a 12 question self-reported scale of GI symptomatology which is widely used and well validated. (205)

Patients with Ulcerative Colitis, similarly had their physical symptoms measured through the Colitis Activity Index which is a self-rated scale of intestinal and extra intestinal symptoms. (206)

5.6 Psychiatric Phenotype

Psychiatric Phenotype was assessed through self-reported symptom scores and self-reports of past psychiatric history, contact with mental health professionals and psychiatric treatment. The HADS scale was chosen due to it being used many times in IBD populations and its clinical utility.

5.7 Mania scales

Mania rating scales can be divided into those used for diagnosis and those used for severity rating. As the main purpose of this study was to capture a range of manic symptoms a scale with a dimensional range of scores was necessary. A study comparing the performance of three self-rating mania scales, The Internal State Scale (ISS), the Self- Report Manic Inventory (SRMI), and the Altman Self-

Rating Mania Scale (ASRM), in a group of patients with acute mania was conducted at different stages of treatment for a group of patients exhibiting mania. In this study patients also were rated by clinicians on the Clinician-Administered Rating Scale for Mania (CARS-M) as a gold standard comparator. At baseline, scores on the
ASRM and the ISS well-being subscale were significantly correlated with CARS-M scores. The sensitivities for each scale to correctly identify patients with acute symptoms were 45% for ISS, 86% for SRMI, and 93% for ASRM.
Specificities were 73%, 46.6%, and 33%. Hence ASRM and SRMI were more sensitive than the ISS in screening patients with acute mania and all three measures appeared sensitive to treatment effects. The ARSM is notably a short scale which was piloted on several out patients and found to be both useable and acceptable. (214)

5.8 Background Psychiatric Data

Psychiatric History was gathered by self-report. Although this is likely to show underreporting, given the constraints and ethical scope of the study it was impossible to gain confirmatory data from primary or secondary care case notes. Below is the form which was used to collect background psychiatric data.

Have you ever been to your doctor with emotional problems or illnesses which may relate to stress?	Yes/No
Have you ever suffered from?	
Depression	Yes/No
An Anxiety Illness	Yes/No
Panic Disorder	Yes/No
Phobias	Yes/No
Obsessive Compulsive Disorder	Yes/No
Manic Depression or Bipolar Illness	Yes/No
Have you ever?	
Been prescribed medication to help you sleep	Yes/No
Been prescribed medication for depression	Yes/No
Been prescribed medication for anxiety	Yes/No
Been prescribed medication for Bipolar Illness	Yes/No
Seen a counsellor	Yes/No
Seen a Psychologist	Yes/No
Seen a Psychotherapist	Yes/No
Seen a Psychiatrist	Yes/No
Been a patient in a Psychiatric Hospital	Yes/No

5.9 Medication history

Medication history was taken from self-report and patient case records. All patients who described being on medication had case records checked for type and dose.

5.10 Inflammatory markers

Patients had routine serology completed while attending the out-patient clinic. Samples were not collected systematically; 466 patients had a Full Blood Count taken of which White Cell Count and Haemoglobin were recorded for this study; 196 had ESR, 364 had CRP and 56 gave samples for Faecal Calprotectin. Patients who completed these tests were more likely to be those experiencing relapse or whose remission was being closely monitored.

5.11 Ethics and R&D

Ethical permission was sought from the Lothian Research and Ethics Committee and R&D approval was sanctioned by NHS Lothian. **08/S1101/58.** Below is a flow chart for recruitment into the study and management of psychiatric outcomes.

5.12 Aims and Hypotheses

The aim of the ISA study was to find predictors of depression and anxiety in a population of out patients with Inflammatory Bowel Disease.

The main hypotheses were that the following factors would predict likelihood of depression and anxiety:

Demographic factors (e.g. age, gender and social class)
Clinical factors (e.g. duration of disease, disease phenotype previous surgery)
Medication (e.g. dose and duration of corticosteroids, infliximab)
Past Psychiatric illness (e.g. previously diagnosed or treated depression)
Inflammatory markers (e.g. CRP, ESR, WCC or calprotectin)

The study sought to find which of these factors were independent.

5.13 Statistics

Data was analysed using SPSS statistical package v19.

Statistical Plan

Demographic information (gender, marital status, employment status), Medical history (disease type, surgery), prescription of medication, past psychiatric illnesses (diagnosis and treatments) were all considered as categorical variables. Dose of corticosteroids, inflammatory markers were continuous variables. Inflammatory markers were normally distributed. Social class was considered as ordinal data. Psychiatric rating scales were considered as ordinal data.

The cohort is described according to frequencies of demographic and clinical information in their respective categories. Comparison of diagnoses and demographic data is performed using Kruksal wallis test and Chi squared tests.

Range of inflammatory markers will be described using means and standard deviations.

Demographic, clinical and medication data will be correlated against psychiatric rating scales using Mann Whitney U tests (binary) and Kruksal Wallis tests (multiple categories).

Predictors of psychiatric scale outcomes will be measured by Independent T tests (binary categories such as gender), Pearson correlations (for continuous measures) such as age) and one-way ANOVAs (multiple categories such as Vienna classification).

Pearson correlations are then used to consider correlations between two sets of continuous variables such as inflammatory markers, psychiatric symptom scales and gastrointestinal symptom scales.

Multivariate linear regression analysis was used to identify the most important independent predictors of HADS anxiety and depression. All significant predictors were entered into the regression model for Crohn's Disease or Ulcerative Colitis and HADS Anxiety or Depression. A forward stepwise model was then used to assess significance of independent variables.

6.0 Results

The following chapter will report the results of the thesis. This will be divided into three main sections. Firstly, there will be a description of the cohort in terms of sociodemographic, psychiatric, medical and other clinical variables. (6.1) Secondly there will be the sociodemographic, clinical and medication predictors of affective disorder including multivariable analysis. (6.2) Thirdly there will be sociodemographic predictors of physical symptoms and inflammatory markers. (6.3)

6.1 Cohort Description

6.1.1 Sociodemographic Characteristics of ISA Cohort

The following section will describe the sociodemographic characteristics of the cohort by diagnosis. This will be a comparison of subjects with Ulcerative Colitis, Crohn's Disease and Coeliac Disease.

6.1.1.1 Gender of Subjects by Diagnosis

	Diagnosis			Total
	Ulcerative Colitis	Crohn's Disease	Coeliac Disease	
Male (%)	115 (45.2)	132 (40.1)	23 (29.4)	270
Female (%)	139 (54.8)	191 (59.9)	55 (60.6)	385
Total	254(100)	323(100)	78(100)	655

6.1.1.2 Marital Status of Subjects by Diagnosis

	Diagnosis			Total
	Ulcerative Colitis	Crohn's Disease	Coeliac Disease	
Married (%)	137 (54.8)	133 (41.8)	43 (55.1)	313
Single (%)	86 (34.4)	153 (48.8)	23 (29.5)	262
Divorced (%)	18 (7.2)	25 (7.9)	8 (10.2)	51
Widowed (%)	9 (3.6)	7 (2.2)	4 (5.1)	20
Total	250(100)	318(100)	78(100)	646

6.1.1.6.1.1.3 Household Composition of subjects by Diagnosis

Household composition: Subject is living with	Diagnosis			Total
	Ulcerative Colitis	Crohn's Disease	Coeliac Disease	
Parents	16(6.4)	42(13.2)	4(5.1)	62
Spouse/Partner	103(41.2)	101(31.8)	30(38.5)	234
Spouse/Partner and Children	75(30.0)	83(26.1)	22(28.2)	180
Children Alone	15 (6.0)	21(6.6)	3(3.8)	39
Flatmate (s)	9(3.6)	17(5.3)	3(3.8)	29
Alone	32(12.8)	54(16.9)	16(20.5)	102
Total	250	318	78	646

6.1.1.4 Employment Status by Diagnosis

	Diagnosis			Total
	Ulcerative Colitis	Crohn's Disease	Coeliac Disease	
Employed	162 (65.1)	185 (58.7)	40 (53.3)	387
Self Employed	21 (8.4)	18 (5.7)	7 (9.3)	46
Unemployed	29 (11.6)	62 (19.5)	8 (10.7)	99
Retired	37 (14.9)	50 (16.7)	20 (26.7)	107
Total	249	315	75	639

6.1.1.5 Incapacity Benefit status by Diagnosis

Incapacity Benefit (ICB)	Diagnosis			Total
	Ulcerative Colitis	Crohn's Disease	Coeliac Disease	
Presently on ICB (%)	18 (7.7)	36 (12)	6 (8.2)	60
Previously on ICB but not now (%)	19 (8.2)	39 (13)	3 (4.1)	61
Never been on ICB (%)	196(84.1)	225 (75.0)	65 (87.7)	486
Total	233	300	74	607

6.1.1.6 Smoking status by Diagnosis

Smoking Status	Diagnosis			Total
	Ulcerative Colitis	Crohn's Disease	Coeliac Disease	
Presently Smoking (%)	48(18.9)	115(35.6)	19(24.4)	182
Past Smoker (%)	71(27.9)	57(17.6)	10(12.8)	138
Never Smoked (%)	135(53.1)	151(46.7)	49(62.8)	335
Total	254(100)	323(100)	78(100)	655

6.1.1.7 Alcohol Consumption by Diagnosis

	Diagnosis			Total
	Ulcerative Colitis	Crohn's Disease	Coeliac Disease	
Presently drinking alcohol	189(74.4)	223(69.0)	57(73.0)	469
Not drinking alcohol	65(25.6)	100(31.0)	21(26.9)	186
Total	254(100)	323(100)	78(100)	655

6.1.1.8 Number of Units of Alcohol Consumed each week by diagnosis

Alcohol Consumption by Units/Week	Diagnosis			Total
	Ulcerative Colitis	Crohn's Disease	Coeliac Disease	
No Alcohol	71(28.0)	127(39.3)	27(34.6)	225
1-5 Units (%)	64(25.2)	107(33.1)	23(29.5)	194
6-15 Units (%)	101(39.8)	77(23.8)	25(32.1)	203
15+ Units (%)	18(7.1)	12(3.7)	3(3.8)	33
Total (%)	254(100)	323(100)	78(100)	655

6.1.1.9 Comparison of Sociodemographic variables by Diagnosis

Using the Kruksal Wallis test, at a significance level of $p<0.05$, marital status, gender, Incapacity Benefit status and smoking status are significantly different between diagnoses. Patients with Crohn's Disease appear less likely to be married and more likely to be single. More patients with Crohn's are female. There appears to be no significant differences in terms of household composition, though the numbers are low in some cell counts. Patients with Crohn's disease are more likely to be or have been on Income Capacity Benefit. Patients with Crohn's disease are more likely to smoke (almost twice as likely 35.6% vs 18.9%) than Ulcerative Colitis patients.

Comparison by Diagnosis Analysis of Variance	Gender	Marital Status	Household Composition	Employment Status	Incapacity Benefit status	Smoking Status	Alcohol Status
Chi-Square (F)	6.163	6.656	1.100	5.244	9.486	11.574	2.107
Significance (P Value)	**0.046**	**0.036**	0.577	0.073	**0.009**	**0.003**	0.349

Using a one-way Anova test, units of alcohol per week were compared between diagnoses. There exists a significant difference between diagnoses.

	Sum of Squares	df	Mean Square	F	Sig. P value
Between Groups	333.676	2	166.838	3.847	
Within Groups	28276.040	652	43.368		**0.022**
Total	28609.716	654			

When Ulcerative Colitis is compared with Crohn's Disease subjects with UC drink significantly more than those with Crohn's Disease. (T test)

	Diagnosis	N	Mean	Std. Deviation	Significance
Units of alcohol per week	Ulcerative Colitis	254	5.31	5.804	**0.005**
	Crohn's Disease	323	3.78	7.334	

6.1.2 Disease characteristics of the ISA cohort

The following subsection of results will describe the disease characteristics of patients in the ISA cohort. This will be done separately for those with Crohn's disease and Ulcerative Colitis. Of 577 patients in the ISA cohort, 293 had been assessed continuously prior to their psychiatric assessment. Patients had gastroenterological phenotyping at diagnosis and at subsequent follow ups.

The follow up assessments occurred between 2000 and 2010. These assessments do not represent specific time points during IBD.

The data will be presented in 2 categories:

6.1.2.1 Clinical and surgical features of IBD subjects

6.1.2.2 Disease phenotyping at ISA assessment

6.1.2.1.1 Clinical features of Crohn's Disease subjects

Of the 323 patients with Crohn's disease who were assessed in 2010-2011, 172 were followed from their original diagnosis which was made between 2001-2003. During this time their IBD phenotype may have altered. The rational here is to consider whether early disease phenotype may predict later psychiatric phenotype.

These 172 patients will be described according to their initial presentation of Crohn's disease and subsequent GI phenotyping. There exist two classification systems of Crohn's disease; Vienna classification and Montreal Classification as described in previous chapters. Below is a table summarising how such classification is performed. Subjects from the ISA cohort were classified according to both systems.

	Vienna	**Montreal**
Age at diagnosis	A1 below 40 y	A1 below 16 y
	A2 above 40 y	A2 between 17 and 40 y
		A3 above 40 y
Location	L1 ileal	L1 ileal
	L2 colonic	L2 colonic
	L3 ileocolonic	L3 ileocolonic
	L4 upper	L4 isolated upper disease*
Behaviour	B1 non-stricturing, non-penetrating	B1 non-stricturing, non-penetrating
	B2 stricturing	B2 stricturing
	B3 penetrating	B3 penetrating
		p perianal disease modifier†

6.1.2.1.2 Disease onset, family history and age at psychiatric assessment of Crohn's Disease subjects

The following table shows age at diagnosis and at the time of psychiatric assessment

	N	Minimum	Maximum	Mean	Std. Deviation
Age at time of ISA Assessment	172	21.2	65.6	44.4	13.392
Age at Diagnosis	172	8.75	64.67	27.08	11.43

The following table shows age at Diagnosis by age category

Age at diagnosis	Frequency	Percent
<12 years	6	3.4
12-18 years	29	16.9
19-29 years	74	43.0
30-39 years	24	14.0
40-49 years	16	9.3
>50	23	13.3
Total	172	100.0

The following shows whether subjects had a family history of Crohn's disease.

Family history	Frequency	Percent
No	132	76.7
Yes	40	23.3
Total	172	100.0

6.1.2.1.3 Disease phenotype by site of disease at diagnosis and follow up

The following table shows anatomical site of disease in patients at diagnosis and follow up.

Site of Disease	At Diagnosis		At Follow Up		Percentage change %
	Present (%)	Absent (%)	Present (%)	Absent (%)	
Oral	8 (4.7)	164 (95.3)	9 (5.2)	163 (94.8)	+0.5
Oesophageal/Gastric	7 (4.1)	165 (95.9)	14 (8.1)	158 (91.9)	+4.0
Jejunum	6 (3.5)	166 (96.5)	18 (10.5)	154 (89.5)	+7.0
Ileum	99 (57.6)	73 (42.4)	125 (72.5)	47 (27.3)	+14.9
Colon	80 (46.5)	92 (53.5)	100 (58.1)	72 (41.9)	+11.6
Rectum	48 (27.9)	124 (72.1)	69 (40.1)	103 (59.9)	+12.2
Anal/Perianal	30 (17.4)	142 (82.6)	57 (33.1)	115 (66.9)	+15.7

6.1.2.1.4 Classification of patients with Crohn's Disease

The following table shows disease classification by Vienna and Montreal Classification system.

	At Diagnosis		At Follow Up	
	Vienna N (%)	Montreal N (%)	Vienna N (%)	Montreal N (%)
Age at Diagnosis	A1 133 (77.3)	A1 13 (7.6)	A1 133 (77.3)	A1 13 (7.6)
		A2 120 (69.7)		A2 120 (69.7)
	A2 39 (22.7)	A3 39 (22.7)	A2 39 (22.7)	A3 39 (22.7)
Location	L1 ileal	L1 53 (30.8) L1+L4 10 (5.8)	L1 ileal	L1 ileal
	L2 colonic	L2 46 (26.7) L2+L4 2 (1.2)	L2 colonic	L2 colonic
	L3 ileocolonic	L3 41 (23.8)	L3 ileocolonic	L3 ileocolonic
	L4 upper	L4 7 (4.1)	L4 upper	L4 isolated upper disease*
Behaviour	B1 114 (66.3)	B1 116 (67.4) B1p 14 (8.1)	B1 58 (33.7)	B1 60 (34.9) B1p 25 (14.5)
	B2 20 (11.6)	B2 19 (11.0)	B2 40 (23.3)	B2 35 (20.3) B2p 9 (5.2)
	B3 23 (13.4)	B3 8 (4.7)	B3 70 (40.7)	B3 30 (17.4) B3p 8 (4.7)

6.1.2.1.5 Surgical History of patients with Crohn's Disease

The following two tables show the surgical history of Crohn's disease patients. This includes a first table showing those with Stomas and a second table showing all procedures.

	Ileal Stoma (%)	Colonic Stoma (%)	Any stoma (%)
Yes	17 (9.9)	1 (0.6)	18 (10.5)
No	155 (90.1)	171 (99.4)	154 (89.5)
Total	172 (100)	172 (100)	172 (100)

Procedure		**Yes (%)**	**No (%)**	**Unknown**	**Total**
Bowel Resection		97 (56.4)	75 (43.6)		172
Number of Bowel Resections	1	57 (33.1)			
	2	21 (12.2)			
	3	12 (7.0)			
	>3	6 (3.5)			
Stricturoplasty		16 (9.3)	154 (89.5)	2 (1.2)	172
Number of Stricturoplasties	1	7 (4.1)			
	2	5 (2.9)			
	3	1 (0.6)			
	>3	3 (1.8)			
Abscess/Fistulae Operation		33 (19.2)	111(64.5)	28 (16.3)	172
Diversion Surgery		10 (5.8)	164 (94.2)		172
Non-Perianal Operations		98 (57.0)	74 (43.0)		172
Number of Non-Perianal Operations	1	48 (27.9)			
	2	18 (10.5)			

	3	15 (8.7)			
	>3	17 (10.0)			
Perianal drainage operations		31 (18.2)	138 (80.2)	3 (1.7)	172
Number of Perianal drainage operations	1	10 (5.8)			
	2	5 (2.9)			
	3	4 (2.3)			
	>3	12 (7.0)			
Therapeutic Surgery		74 (43.0)	98 (57.0)		172
Number of Therapeutic Surgeries	1	55 (32.0)			
	2	22 (12.8)			
	3	14 (8.1)			
	>3	7 (4.0)			

6.1.2.1.6 Clinical features of subjects with Ulcerative Colitis

The following section relates to patients with Ulcerative Colitis. Of 245 patients in the ISA study with Ulcerative colitis, 121 have been followed up from the original cohort.

6.1.2.1.7 Disease onset and family history of Ulcerative Colitis

Below is a table showing age at diagnosis and age at ISA assessment followed by a table showing presence of family history.

	N	Minimum	Maximum	Mean	Std. Deviation
Age at time of ISA Assessment	121	18.5	63.2	47.3	9.4
Age at Diagnosis	121	16.83	65.25	32.2	11.26
Duration of Illness	121	1	53.00	13.2	9.45

Family history	Frequency	Percent
No	103	85.1
Yes	18	14.9
Total	121	100.0

6.1.2.1.10 Surgical and Medical History of patients with Ulcerative Colitis

Below is a table showing surgical history of patients with Ulcerative colitis. Patients with UC frequently have other medical co morbidities which are shown below.

Procedure	Yes N (%)	No N (%)	Missing N (%)	Total N (%)
Colectomy	9 (7.4)	112 (92.6)		121 (100)
Ileo-Anal Pouch	6 (5.0)	115 (95.0)		121 (100)
Pouchitis	2 (1.7)	117 (96.7)	2 (1.7)	121 (100)
Tonsillectomy	28 (23.1)	93 (76.9)		121 (100)
Appendectomy	6 (5.0)	115 (95.0)		121 (100)
Joint Problems	43 (35.5)	78 (64.5)		121 (100)

6.1.2.2.1 Disease phenotyping at ISA assessment

The following section will describe the disease phenotype performed at the time of the ISA assessment. This will include symptom self-reported scores and inflammatory markers.

The following table shows descriptive statistics of measures of disease activity.

	Number of patients	Minimum	Maximum	Mean	Std. Deviation
Colitis Activity Index	254	0	13	3.8386	2.91133
Harvey Bradshaw Index	323	0	10	3.8824	2.68971
C-Reactive Protein (CRP)	316	0	199	8.10	15.621
Erythrocyte Sedimentation Rate (ESR)	196	0	84	14.75	12.849
White Cell Count	461	0	16	7.31	2.407
Faecal Calprotectin	56	0	2500	652.84	717.910
Haemoglobin Hb	466	0	178	135.67	15.354

6.1.3 Psychiatric Phenotype

The following results subsection shows the psychiatric phenotype of the ISA cohort. Subjects were asked about previous psychiatric diagnoses, previous psychiatric medication and previous contact with psychiatric services. Subjects were asked to complete the Hospital Anxiety Depression Scale and the Altman Self Rated Mania Scale.

The following table shows numbers and percentages of patients who report a past history of psychiatric diagnosis, previous psychiatric medication usage and previous contact with psychiatric services. These results are categorised by gastrointestinal diagnosis (Ulcerative Colitis, Crohn's Disease and Coeliac Disease).

Past Psychiatric History		Ulcerative Colitis (%)	Crohn's Disease (%)	Coeliac Disease	Significance (P)
Have you ever suffered from?	Depression	83 (32.7)	102 (31.6)	26 (33.3)	0.93
	Anxiety Disorder	53 (20.9)	59 (18.3)	19 (24.4)	0.44
	Panic Disorder	36 (14.2)	32 (9.9)	7 (9.0)	0.21
	Phobias	10 (3.9)	18 (5.6)	3 (3.8)	0.61
	Obsessive Compulsive disorder	14 (5.5)	17 (5.3)	3 (3.8)	0.84
	Bipolar Disorder	1 (0.3)	5 (1.5)	0 (0.0)	0.23
Have you ever been prescribed?	Antidepressant medication	67 (26.4)	80 (24.8)	17 (22.0)	0.71
	Anxiety Medication	36 (14.1)	37 (11.5)	12 (15.4)	0.50
	Bipolar medication	0 (0.0)	3 (0.9)	0 (0.0)	0.21
Have you ever seen?	Counsellor	56 (22.0)	67 (20.7)	19 (24.4)	0.77
	Psychologist	25 (9.8)	38 (11.8)	7 (9.0)	0.66
	Psychotherapist	12 (4.7)	13 (4.0)	4 (5.1)	0.86
	Psychiatrist	22 (8.7)	31(9.6)	3 (3.8)	0.26
	Been a patient in a Psychiatric Hospital	5 (2.0)	4 (1.2)	2 (2.6)	0.65
Total		254 (100)	323 (100)	78 (100)	

The table below compares mean scores on the Hospital Anxiety Depression Scale (HADS) and Altman Self Rated Mania Scale (ARSM) by gastrointestinal diagnosis. These are compared between all three diagnoses and by each pair of diagnoses for significant differences.

	Ulcerative Colitis Mean (StD)	Crohn's Disease Mean (StD)	Coeliac Disease Mean (StD)	Significance between UC and Crohn's (P-value)	Significance between UC and Coeliac (P-value)	Significance between Crohn's and Coeliac (P-value)	One-way ANOVAs Significance
HADS Anxiety (0-21)	6.80 (4.16)	7.25 (4.51)	6.46 (4.51)	0.213	0.544	0.165	0.249
HADS Depression (0-21)	3.87 (3.68)	4.51 (4.07)	3.40 (3.99)	0.049	0.327	**0.030**	0.033
HADS Total (0-42)	10.67 (7.06)	11.70 (7.72)	9.72 (7.67)	0.096	0.309	**0.043**	0.063
Altman Self Rated Mania (0-20)	3.42 (3.41)	3.84 (3.74)	3.50 (3.72)	0.160	0.865	0.466	0.358

Almost one third of patients with these gastrointestinal diagnoses report a previous history of depression. Up to one quarter of these patients have received a psychological intervention or antidepressant medication. There are, however, significant differences in the rates between patients with Coeliac Disease or either inflammatory bowel disease with regards to past psychiatric diagnoses, psychiatric treatments or contact with psychiatric services.

With regards to present psychiatric symptoms, there are no differences between gastrointestinal diagnoses in terms of anxiety symptoms nor mania symptoms. There exists a significant difference with regards to depressive symptoms between Crohn's Disease and

both Ulcerative Colitis and Coeliac Disease where subjects with Crohn's score higher on the HADS-D.

6.1.4 Medication

The following results subsection describes the medication taken by the cohort both presently and in the last year. The results are not categorised by diagnosis.

Medication	*What medication are you taking now?* N (%)	*What medication were you taking in the last year (but not now)?* N (%)
Prednisolone	85 (14.6)	113 (19.6)
Budesonide	20 (3.5)	5 (1.0)
Aminosalicytes (Mesalazine, Asacol, Pentasa Balsalazide)	271 (46.4)	243 (40.2)
Azathioprine	139 (24.1)	48 (8.3)
Mecaptopurine	35 (6.0)	12 (2.1)
Methotrexate	12 (2.1)	7 (1.2)
Infliximab	17 (2.9)	11 (1.9)
Adulimamab	25 (4.3)	7 (1.2)
TOTAL	578 (100)	578 (100)

The following table shows the dose and duration of Prednisolone used.

	Minimum	Maximum	Mean	SD
Dose of Prednisolone	1mg	50mg	18.11	13.63
Weeks of Prednisolone	1 week	1820 weeks	175 weeks	372.4

6.2 Predictors of Affective disorder in subjects with Crohn's disease and Ulcerative colitis

The following section will look at domains of predicting affective disorder. These will be:

6.2.1 Sociodemographic predictors of HADS

6.2.2 Disease predictors

6.2.3 Medication Predictors

6.2.4 Multivariate analysis of predictors of affective disorder

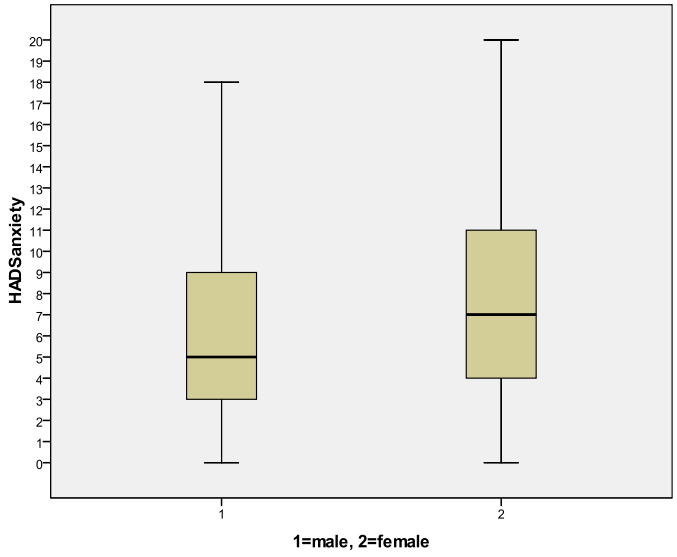
6.2.1 Sociodemographic predictors of Anxiety and Depression from Hospital Anxiety Depression Score (HADS)

The following subsection will look at how socio demographic variables predict affective disorder in this population. Here all IBD patients will be considered as one group and will be analysed by Anxiety and Depression separately.

6.2.1.1 HADS Anxiety

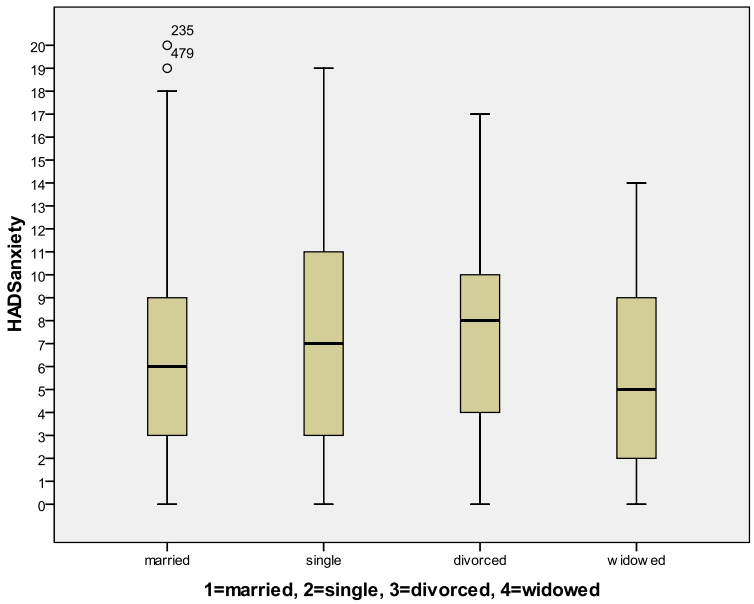
6.2.1.1.1 Gender by HADS anxiety scale

Mann-Whitney U=42973.5, Z=-3.856, Significance p<0.001



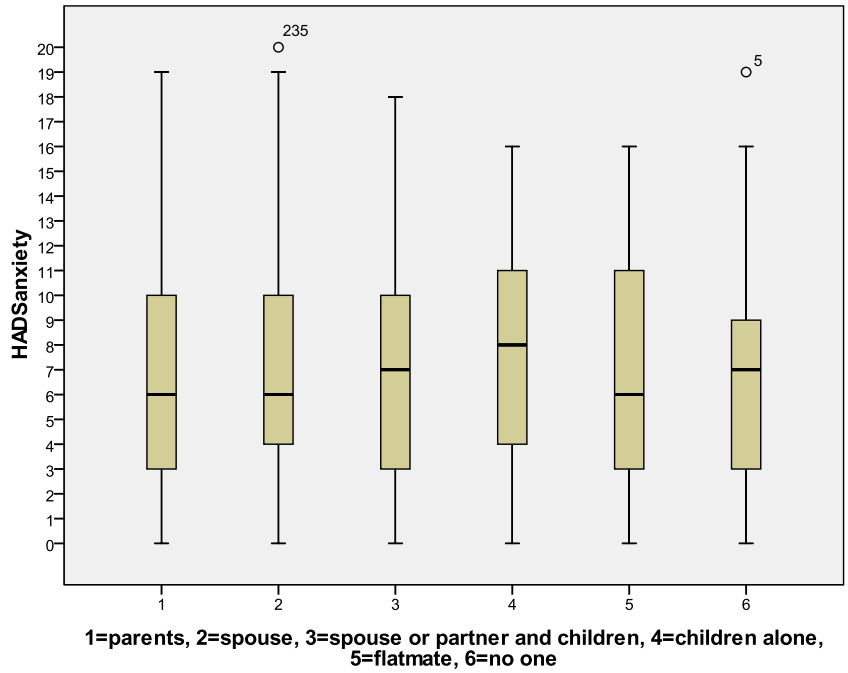
6.2.1.1.2 Marital status by HADS Anxiety

Kruskal Wallis Test Chi-Square =8.679, Significance P=0.034



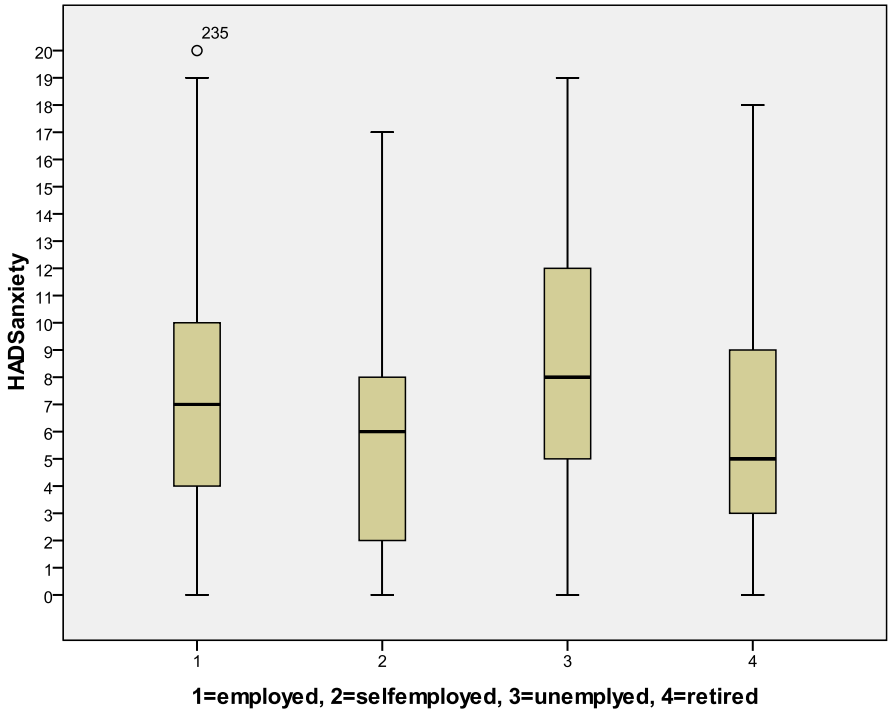
6.2.1.1.3 HADS Anxiety Scores by Household composition

Kruskal Wallis Test, P=0.798



6.2.1.1.4 HADS Anxiety Scores by Employment Status

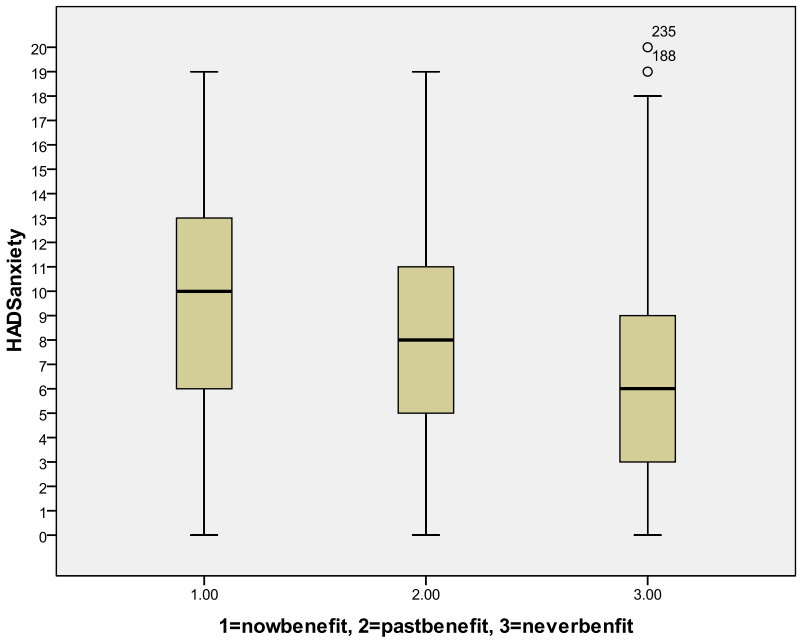
Kruskal Wallis Test, Chi square = 21.549, P<0.001



6.2.1.1.5 HADS Anxiety scores by Incapacity Benefit status

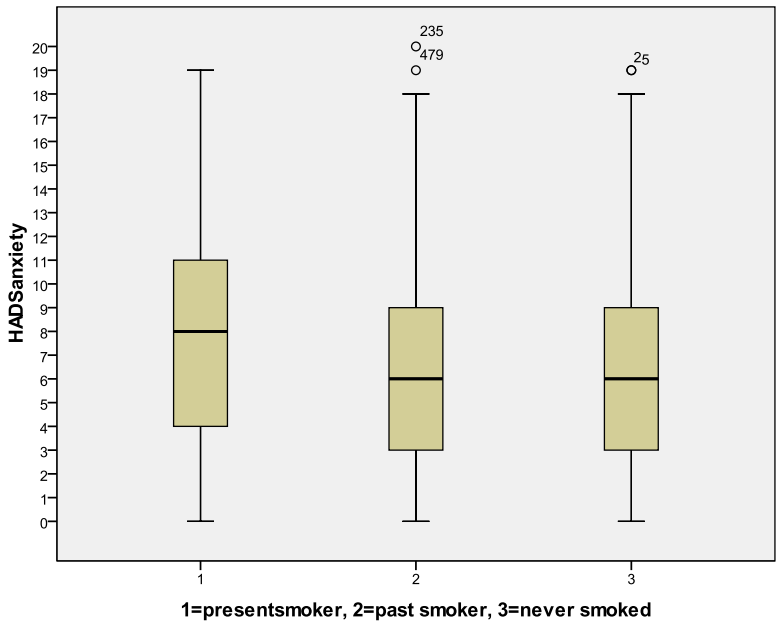
Kruskal Wallis Test

Chi-Square 23.198, Significance P<0.0001



6.2.1.1.6 HADS Anxiety scores by smoking status

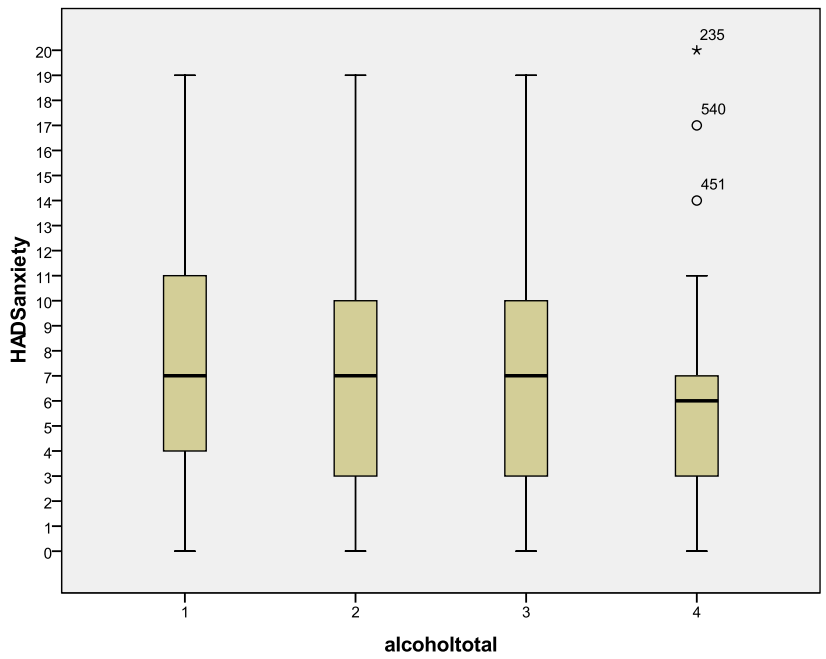
Kruskal Wallis Test Chi-Square =2.246 P=.002



6.2.1.1.7 HADS Anxiety scores by total alcohol intake

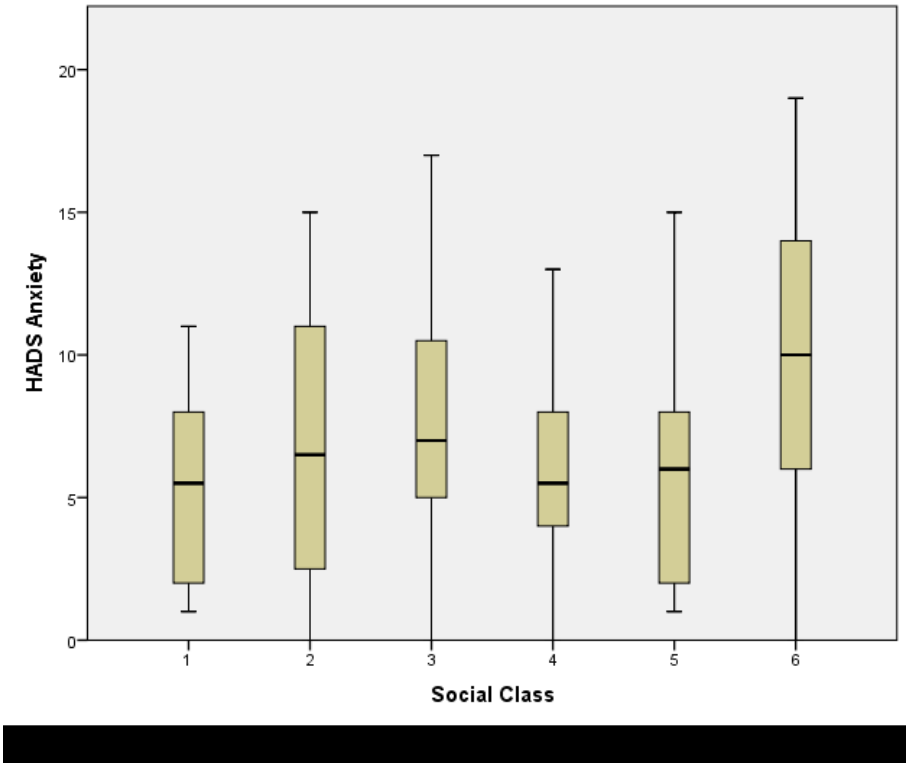
Kruskal Wallis Test Chi-Square=1.985 P=0.575

No alcohol 225 (34.2%)
0-5 Units per week 195 (29.7%)
5-15 Units per week 203 (30.9%)
>15 Units per week 33 (5.0%)



6.2.1.1.8 HADS Anxiety by social class

Anova F=2.84 P<0.018

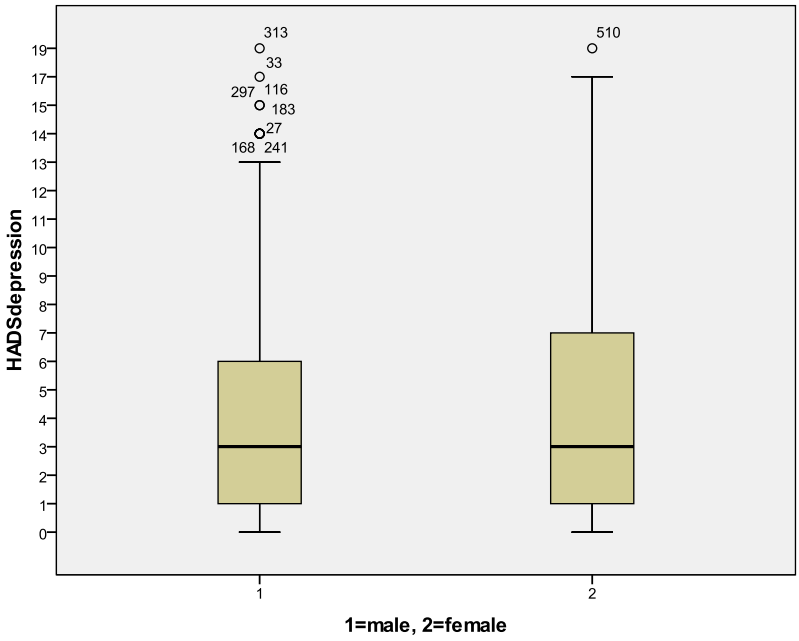


6.2.1.2 HADS Depression scores by sociodemographic variables

The following section will look at HADS depression scores by demographic variables

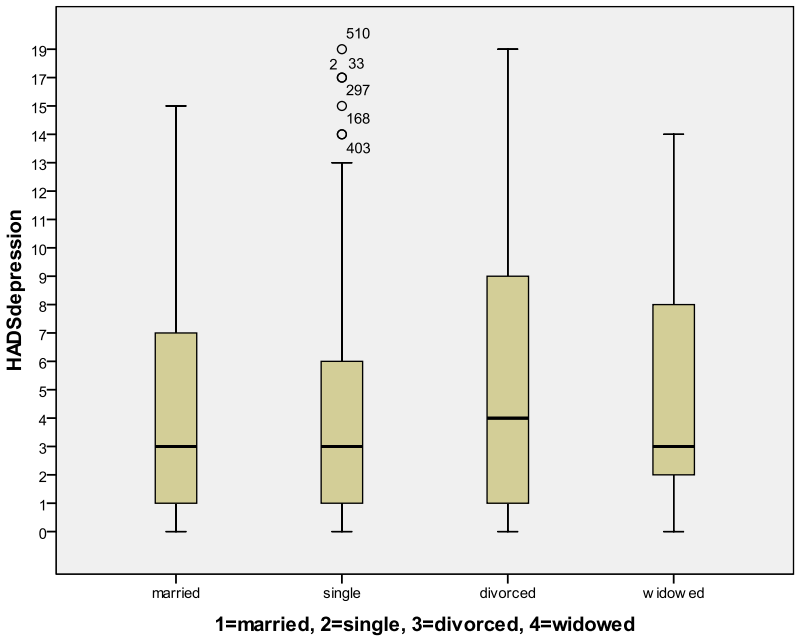
6.2.1.2.1 HADS Depression scores by Gender

Mann-Whitney U=50435.500, Z=-.730, P=0.465



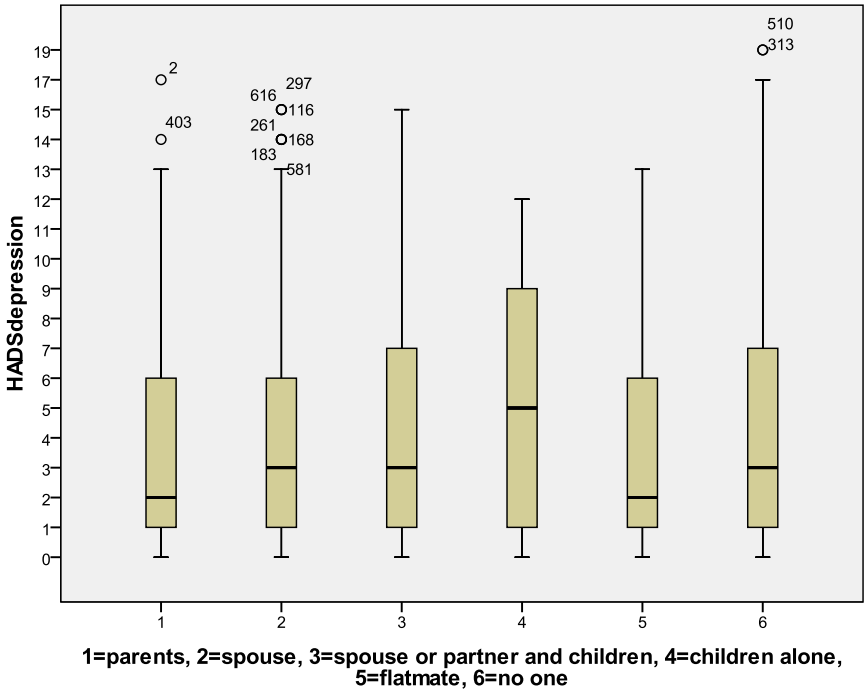
6.2.1.2.2 Depression by marital status

Kruskal Wallis Test chi=1.710, P=0.635



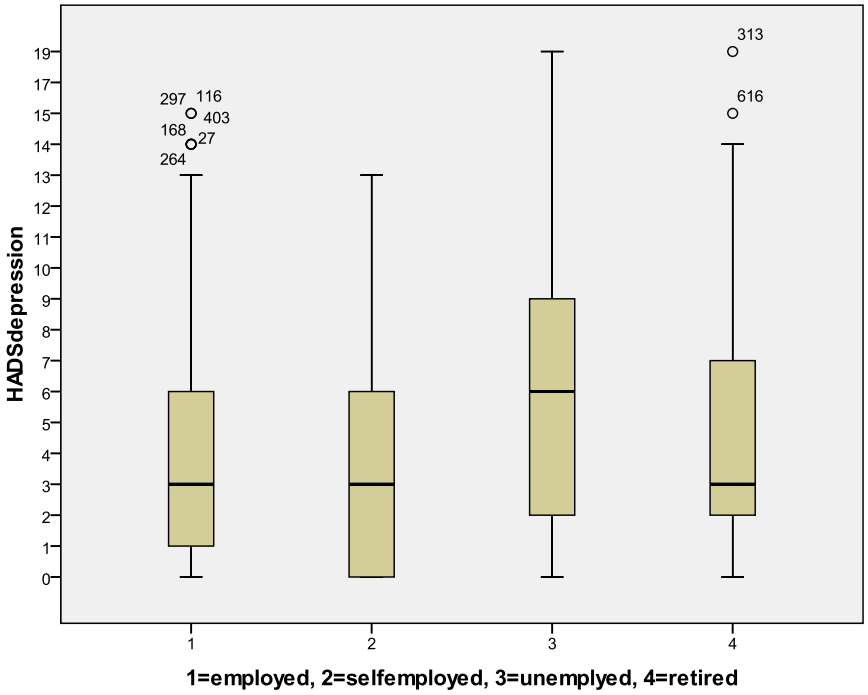
6.2.1.2.3 Depression by household composition

Kruskal Wallis Test 4.297, P=0.507



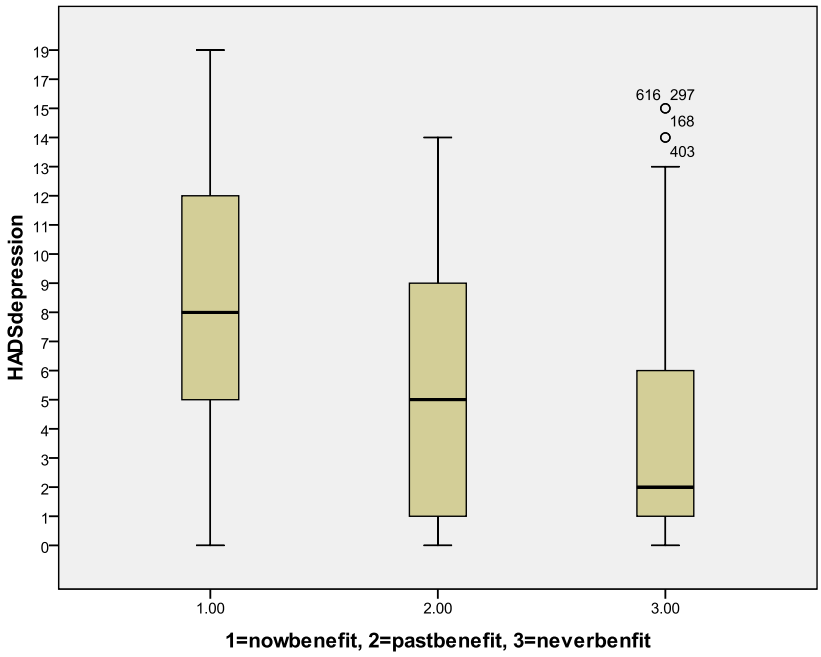
6.2.1.2.4 Depression by Employment status

Kruskal Wallis Test Chi=23.064, P<0.0001



6.2.1.2.5 Depression by Incapacity Benefit Status

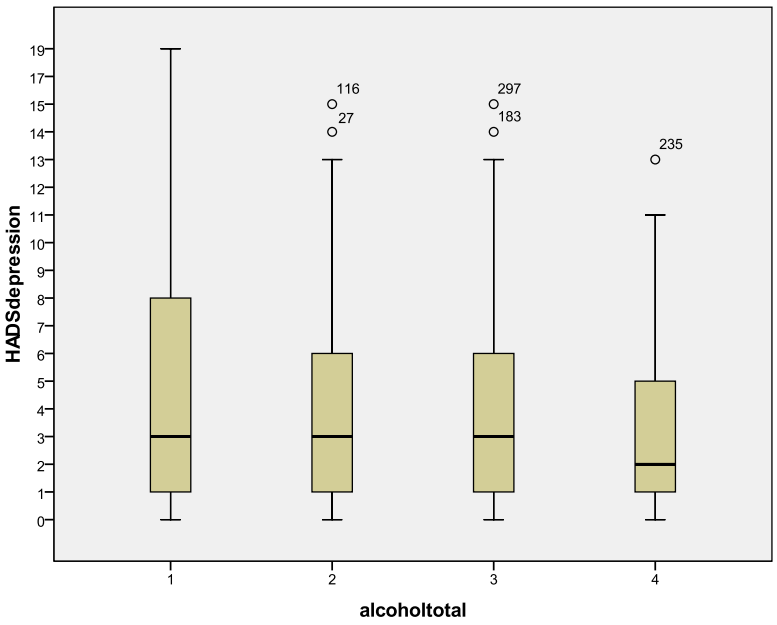
Kruskal Wallis Test, Chi=63.058, P<0.0001



6.2.1.2.6 Depression by Alcohol Units per week

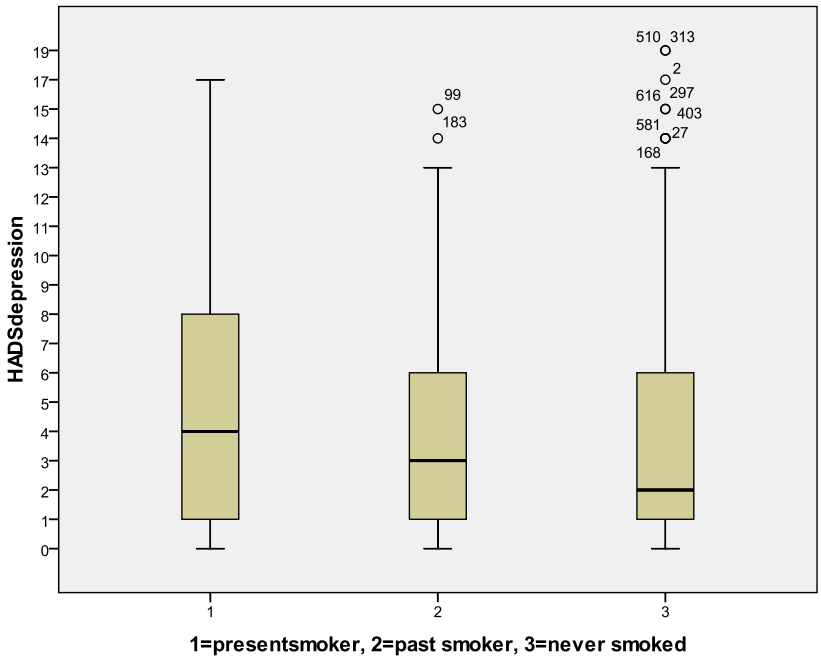
Kruskal Wallis Test, Chi=8.569 p=0.036

No alcohol 225 (34.2%)
0-5 Units per week 195 (29.7%)
5-15 Units per week 203 (30.9%)
>15 Units per week 33 (5.0%)



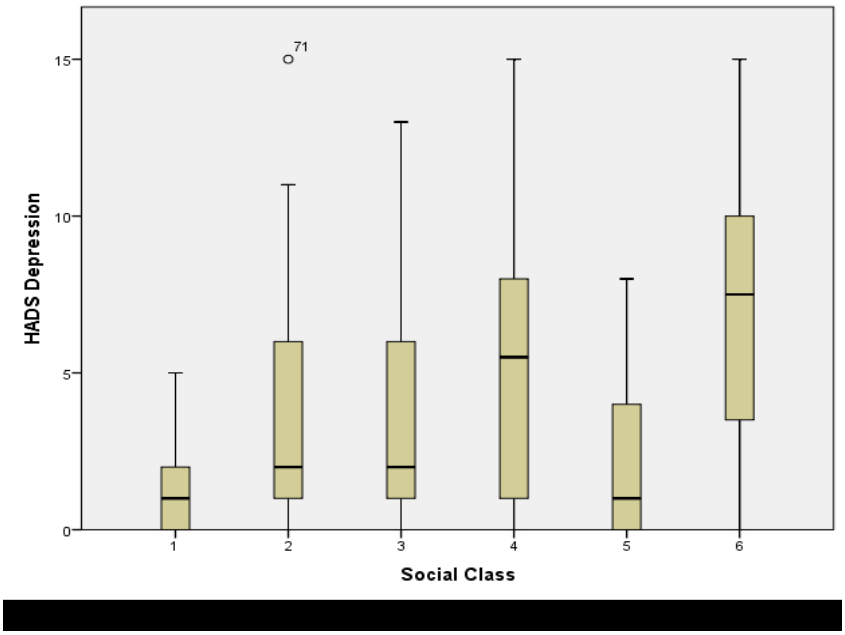
6.2.1.2.7 Depression by Smoking Status

Kruskal Wallis Test, Chi Sq.= 11.965, P=0.003



6.2.1.2.9 Depression by social class

Anova F=4.001 P<0.001



6.2.1.2.10 Summary

In summary the significant predictors of Anxiety are:

Gender*, Marital Status, Smoking, Incapacity Benefit*, Employment Status*, Social class

The Significant predictors of Depression are:

Smoking, Alcohol Consumption, Incapacity Benefit*, Employment Status*, Social Class

* = Significance where P<0.0001

6.2.2 Disease predictors of affective disorders

The following subsection of results will relate to whether disease phenotype may predict psychiatric phenotype. This will be initially divided into Crohn's Disease and Ulcerative colitis.

6.2.2.1 Crohn's Disease

Disease phenotype will be described by several factors. These are; age at which the subject was diagnosed with the disease, whether the subject was diagnosed before or after the age of 18, whether the subject has suffered from the illness for than 10 years and whether there is a family history of Crohn's Disease. The second component of the phenotyping will relate to the site of disease at diagnosis and follow up and the Vienna Classification of the disease at diagnosis and follow up.

The psychiatric phenotype will be defined in three ways. Firstly, the present level of affective disorder symptoms as measured by the HADS. Secondly, the past psychiatric history and thirdly by the reported use of psychiatric/psychological therapies.

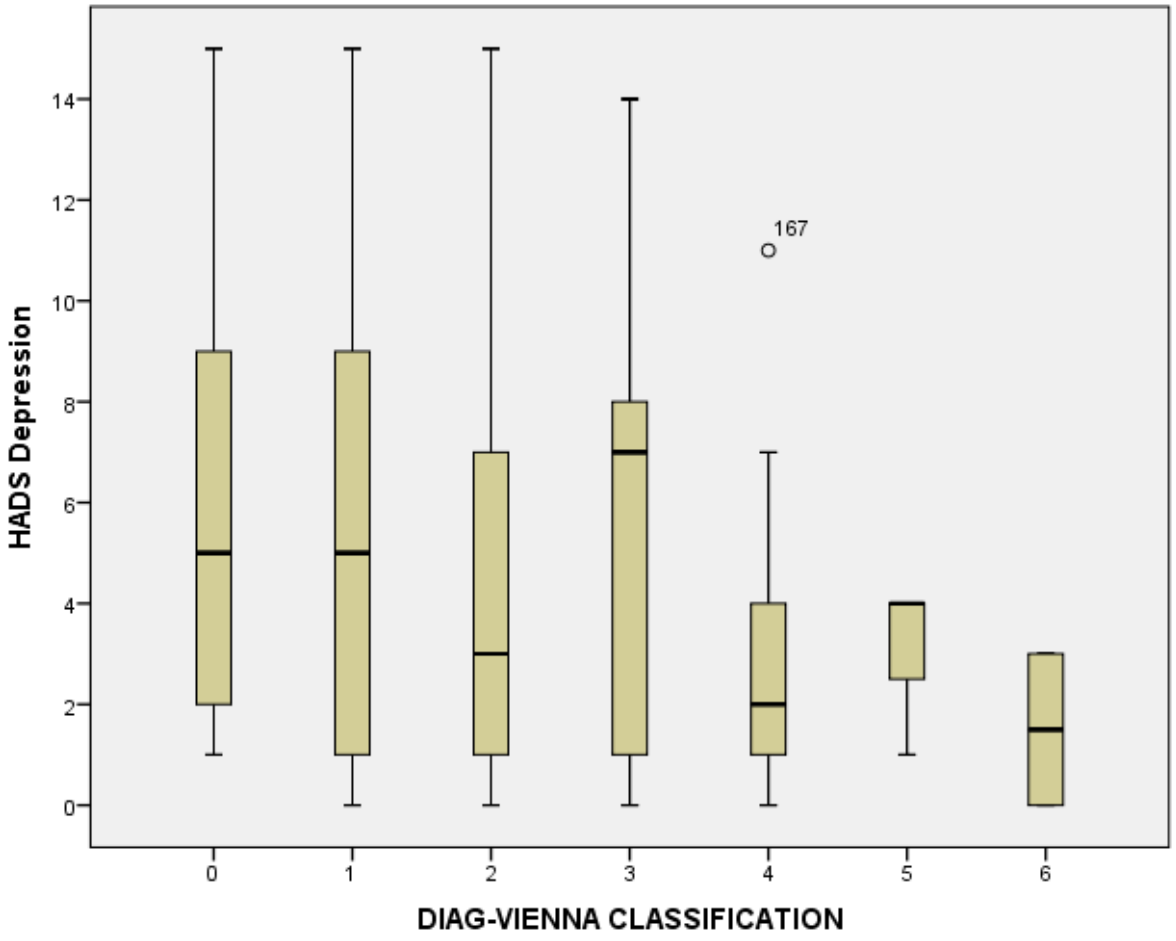
The psychiatric phenotype will then be correlated with the surgical history of the subjects. Finally, the psychiatric phenotype will be compared with the present inflammatory markers; White Cell Count, Erythrocyte Sedimentation Rate, C-Reactive Protein and Haemoglobin. These will all be correlated with the present gastroenterological symptoms of the subjects as measured by the Harvey Bradshaw Index.

6.2.2.1.1 Crohn's Disease features and classification and psychiatric phenotype (HADS and self-report)

The first table below shows Crohn's phenotype and present affective symptoms as measured by HADS.

Disease Phenotype Variable	Statistical Test	Number of Subjects	HADS Anxiety Significance (P)	HADS Depression Significance (P)
Age at Diagnosis	*Pearson Correlation*	172	P=0.620	P=0.019
Onset of Illness Below 18 years	*Independent T-test*	35 <=18years 128 >18years	P=0.736	**P=0.060**
Duration of years of illness </> 10 years	*Independent T-test*	62 > 10years 110 < 10years	**P=0.063**	**P=0.006**
Family History of IBD	*Independent T-test*	132 No FH 40 with FH	P=0.312	P=0.312
Site of Illness at Diagnosis	*Independent T-test*			
Oral		8yes 164 no	P=0.354	**P=0.061**
Ileum		73 yes 99 no	P=0.143	P=0.202
Colon		92 yes 80 no	P=0.895	P=0.820
Rectum		48 yes 124 no	P=0.990	P=0.366
Anal/Perianal		30 yes 142 no	P=0.343	P=0.176
Classification of Illness at Diagnosis (Vienna)	*One-way ANOVAs*	172	F=1.549 P=0.165	F=1.543 P=0.167
Site of Illness at Follow Up	*Independent t test*			
Oral		9 yes 163 no	P=0.182	**P=0.033**
Ileum		47 yes 125 no	P=0.474	P=0.474
Colon		72 yes 100 no	P=0.960	P=0.890
Rectum		103 yes 63 no	P=0.679	P=0.286
Anal/Perianal		115 yes 57 no	P=0.047	P=0.272
Classification of Illness at Follow Up (Vienna)	*One-way ANOVAs*	172	F=0.911 P=0.461	F=0.951 P=0.488

6.2.2.1.2 The following boxplot shows HADS scores against Vienna Classification of Crohn's at initial diagnosis.



6.2.2.1.3 The Following table shows Crohn's phenotype against past psychiatric history

Disease Phenotype Variable	Number of subjects	Does the Subject have a Past History of				
		Depression	An Anxiety Disorder	Panic Disorder	Phobias	Obsessive Compulsive Disorder
Age at Diagnosis	172	P=0.115	P=0.423	P=0.825	P=0.974	P=0.990
Onset of Illness Below 18 years	38<=18years 134>18years	**P=0.030**	P=0.564	P=0.281	P=0.178	P=0.747
Duration of years of illness	62<10years 110>10years	P=0.439	P=0.303	P=0.644	P=0.222	P=0.982
Family History of IBD	40 with FH 132 without FH	P=0.875	P=0.339	P=0.239	P=0.138	p=0.681
Site of Illness at Diagnosis						
Oral	8 yes 164 no	**P=0.030**				
Ileum	73 yes 99 no	P=0.920	P=0.956	P=0.531	P=0.423	P=0.835
Colon	92 yes 80 no	P=0.492	P=0.785	P=0.962	P=0.566	P=0.942
Rectum	48 yes 124 no	P=0.915	P=0.604	P=0.322	P=0.968	P=0.459
Anal/Perianal	30 yes 142 no	P=0.938	P=0.656	P=0.172	P=0.216	P=0.116
Classification at Diagnosis (Vienna)	172	**P=0.034**	P=0.453	P=0.740	P=0.986	P=0.480
Site of Illness at Follow Up						
Ileum	47 yes 125 no	P=0.277	P=0.811	P=0.347	P=0.348	P=0.488
Colon	72 yes 100 no	P=0.760	P=0.606	P=0.564	P=0.468	P=0.803
Rectum	103 yes 63 no	P=0.778	P=0.712	P=0.540	P=0.349	P=0.794
Anal/Perianal	115 yes 57 no	P=0.409	P=0.574	P=0.068	P=0.281	P=0.371
Classification at Follow Up (Vienna)	172	P=0.175	P=0.280	P=0.817	P=0.959	P=0.885

6.2.2.1.4 The following table shows Crohn's Phenotype by psychiatric treatment.

Disease Phenotype Variable	Number of subjects	Has the subject received the following treatments			
		Antidepressant medication 45 y 128n	Anti Anxiety Medication 20y 152n	Psychological therapy 51y 121n	Psychiatrists 15y 157n
Age at Diagnosis	172	P=0.662	P=0.425	P=0.287	**P=0.001**
Onset of Illness Below 18 years	38<=18years 134>18years	P=0.418	P=0.811	P=0.273	**P<0.0001**
Duration of years of illness	62<10years 110>10years	P=0.246	P=0.113	P=0.062	P=0.430
Family History of IBD	40 with FH 132 without FH	P=0.530	P=0.449	P=0.464	P=0.744
Site at Diagnosis					
Oral	8 yes 164 no	**P=0.086**	P=0.295	P=0.769	**P=0.096**
Ileum	73 yes 99 no	P=0.310	P=0.468	P=0.259	P=0.842
Colon	92 yes 80 no	P=0.711	P=0.079	P=0.447	P=0.580
Rectum	48 yes 124 no	P=0.548	P=0.759	P=0.162	P=0.476
Anal/Perianal	30 yes 142 no	P=0.399	P=0.749	P=0.356	**P=0.091**
Classification at Diagnosis (Vienna)	172	P=0.125	P=0.313	P=0.331	P=0.322
Site at Follow Up					
Oral	9 yes 163 no	**P=0.067**	P=0.265	P=0.617	P=0.141
Ileum	47 yes 125 no	P=0.151	P=0.414	P=0.727	P=0.506
Colon	72 yes 100 no	P=0.769	P=0.509	P=0.258	P=0.213
Rectum	103 yes 63 no	P=0.469	P=0.620	**P=0.026**	P=0.589
Anal/Perianal	115 yes 57 no	P=0.443	P=0.489	**P=0.001**	**P=0.021**
Classification at Follow Up (Vienna)	172	P=0.108	P=0.396	P=0.491	P=0.337

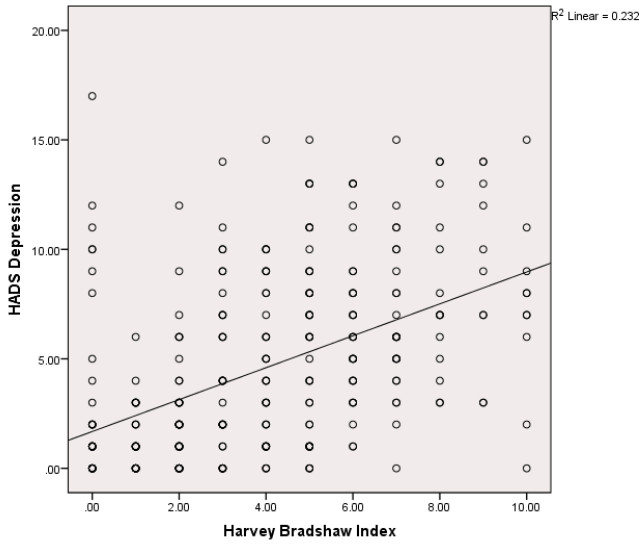
6.2.2.1.5 The following table shows all measures of psychiatric phenotype against surgical history.

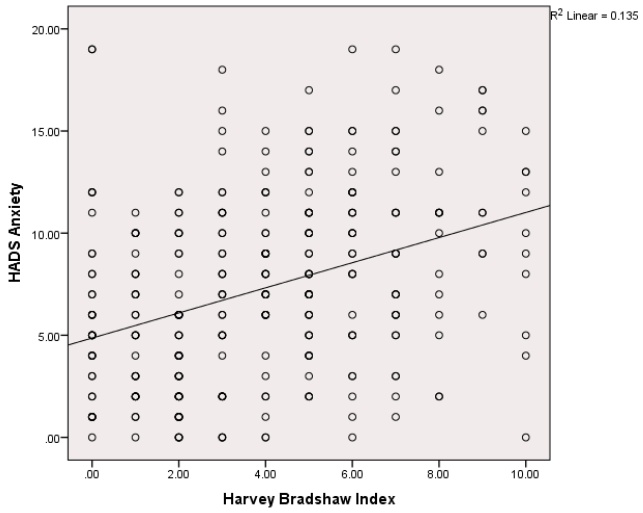
	Bowel Resection	**No. Bowel resections** (0,1,2,3,3+)	**Stricturoplasty**	**Ileal Stoma**	**Non Perianal operations**	**Number of non Perianal operations** (0,1,2,3,3+)	**Therapeutic surgeries**
Number of subjects	97/172	172	16/172	17/172	98/172	172	74/172
HADS A	P=0.232	P=0.237	P=0.147	P=0.783	P=0.148	P=0.854	P=0.098
HADS D	**P=0.032**	**P=0.044**	P=0.410	**P=0.045**	**P=0.033**	P=0.118	**P=0.017**
Depression	P=0.991	P=0.262	P=0.558	P=0.550	P=0.513	P=0.385	P=0.218
Anxiety	P=0.164	P=0.326	P=0.859	P=0.673	P=0.726	**P=0.042**	P=0.056
Antidepressants	P=0.572	P=0.850	P=0.317	P=0.798	P=0.325	P=0.605	P=0.715
Anti-Anxiety	P=0.730	P=0.684	**P=0.037**	P=0.438	P=0.750	P=0.767	P=0.266
Psychological therapy	P=0.354	P=0.600	P=0.584	P=0.274	P=0.418	P=0.316	P=0.370
Psychiatrists	P=0.803	P=0.470	P=0.954	**P=0.023**	P=0.211	P=0.515	P=0.357

6.2.2.1.2 Symptoms and inflammatory markers as predictors of psychiatric phenotype in subjects with Crohn's disease

The following section will look at self-reported symptom measures (Harvey Bradshaw Index), Inflammatory Markers (CRP, ESR, WCC, Calprotectin and Hb) and Psychiatric phenotype (HADS, past psychiatric history).

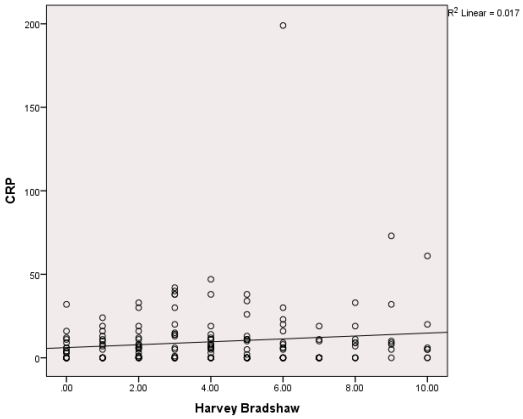
6.2.2.1.2.1 The following graphs show correlation of HBI against HADS depression and anxiety for 323 subjects with Crohn's disease

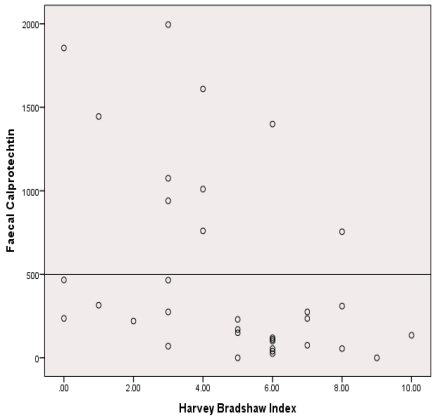


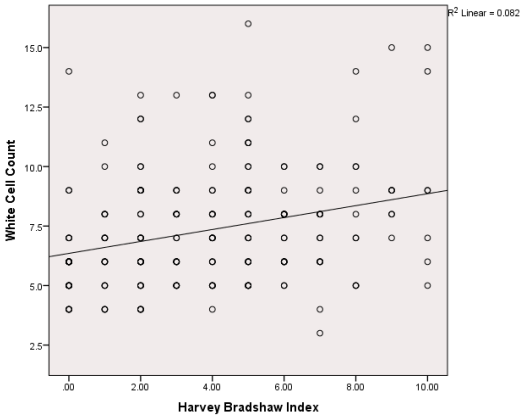


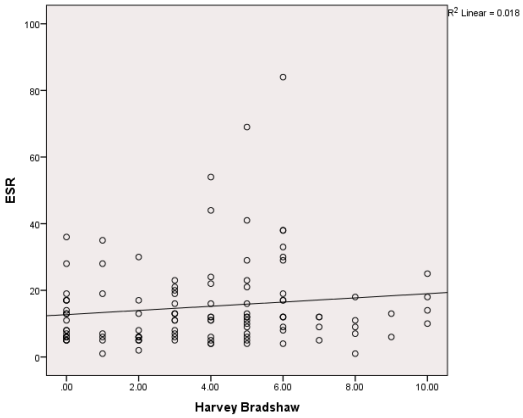
Depression: Pearson correlation 0.482, Significance P<0.0001, Anxiety: Pearson Correlation 0.368, Significance P>0.0001,

6.2.2.1.2.2 Harvey Bradshaw Index against Inflammatory Markers





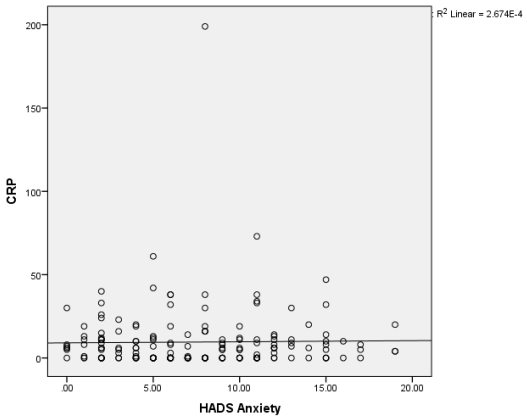


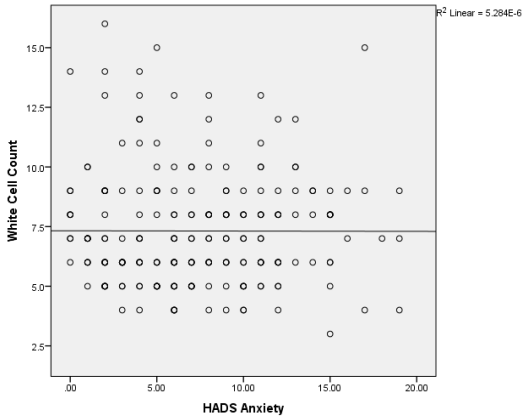


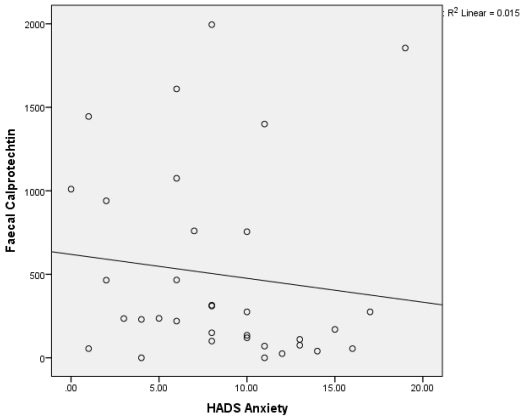
Inflammatory Marker	CRP	ESR	WCC	Faecal Calprotectin
Pearson Correlation	0.131	0.132	0.286**	-0.431*
Significance (P)	0.081	0.162	0.000	0.011
Number of Subjects	180	113	225	34

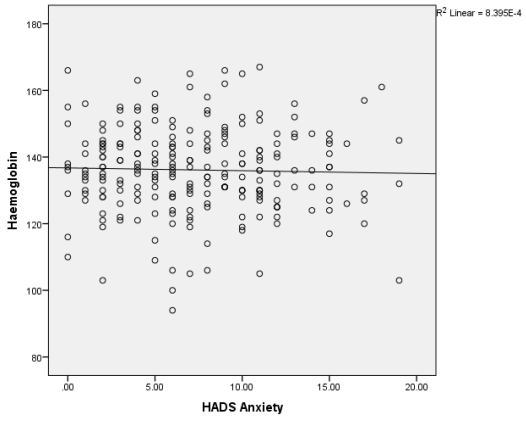
Here it can be seen that HBI index correlates significantly with White cell count and Faecal Calprotectin.

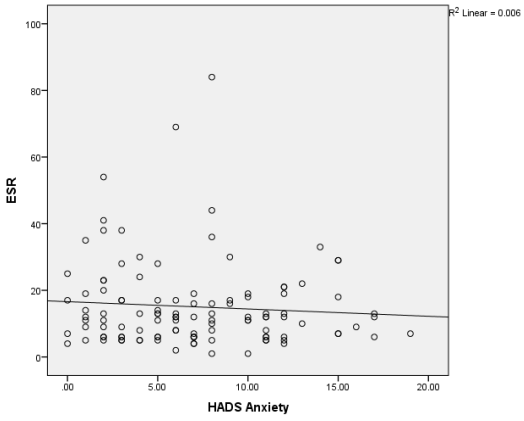
6.2.2.1.2.3 The following graphs show the relationship between HADS Anxiety and inflammatory markers. Here there are no significant correlations



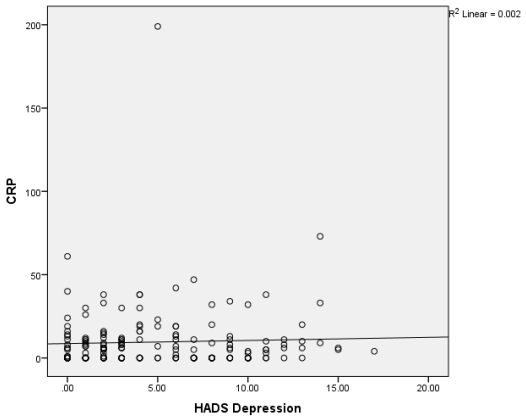




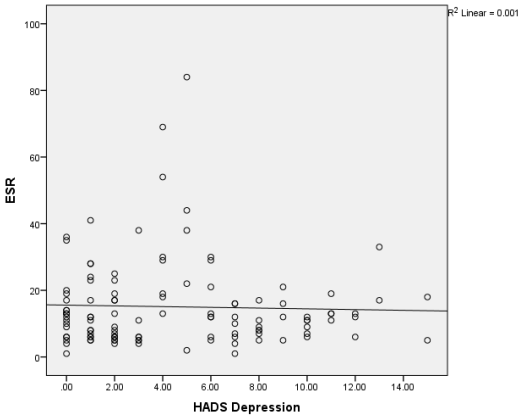


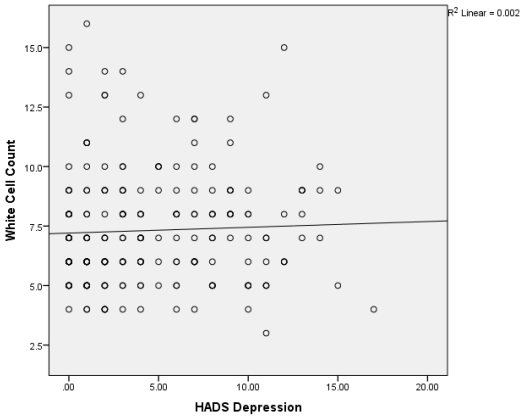


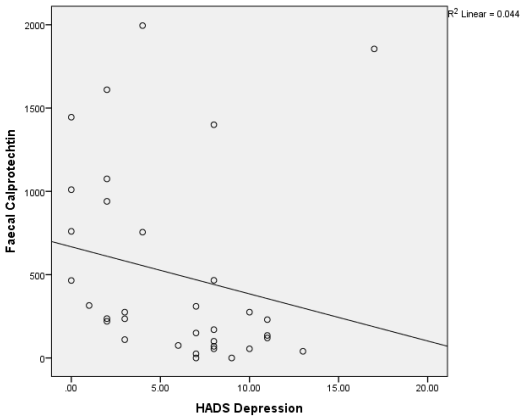
Inflammatory Marker	CRP	ESR	WCC	Faecal Calprotectin	Haemoglobin
Pearson Correlation	0.016	-0.078	-0.002	-0.120	-0.029
Sig. (2-tailed)	0.828	0.415	0.973	0.498	0.663
Number of subjects	180	113	225	34	229

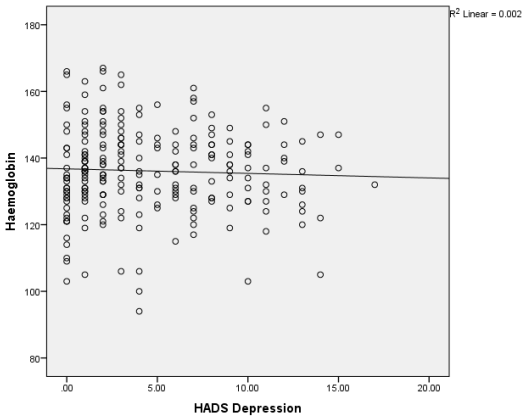


6.2.2.1.2.4 The following graphs show the relationship between HADS Depression and inflammatory markers. Here there are no significant correlations.



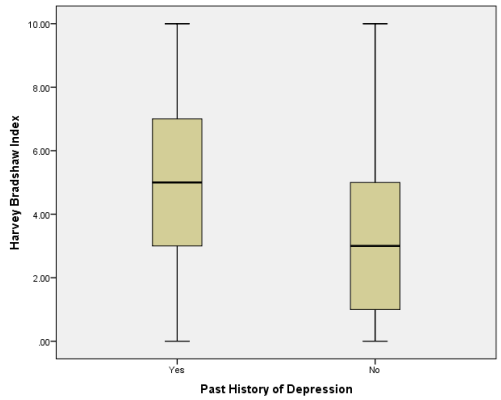


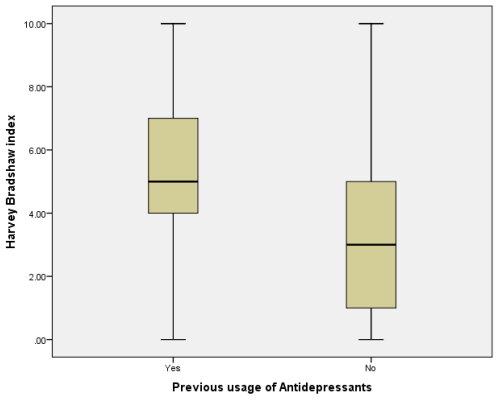


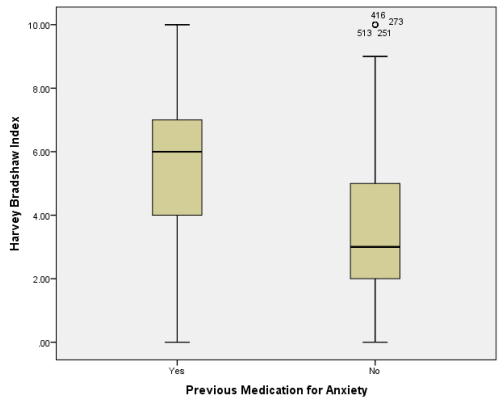


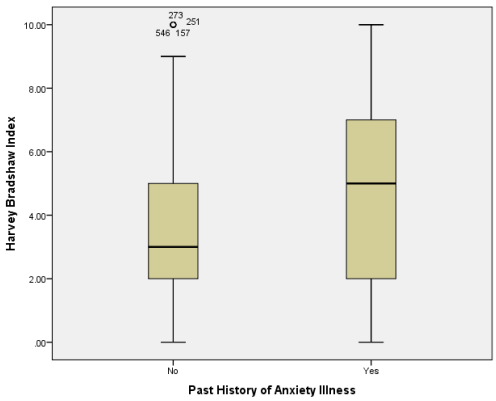
Inflammatory Marker	CRP	ESR	WCC	Faecal Calprotectin	Haemoglobin
Pearson Correlation	0.042	-0.035	0.041	-0.209	-0.043
Sig. (2-tailed)	0.579	0.716	0.538	0.235	0.517
Number of subjects	180	113	225	34	229

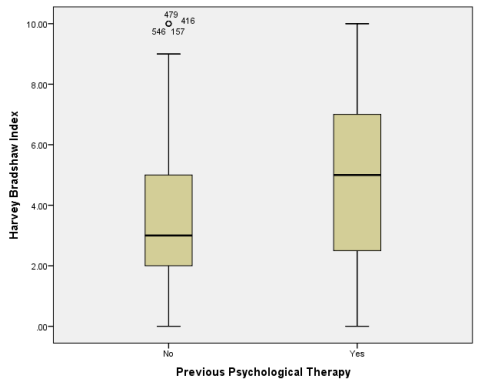
6.2.2.1.2.5 The following graphs show present gastrointestinal symptoms against past psychiatric history.

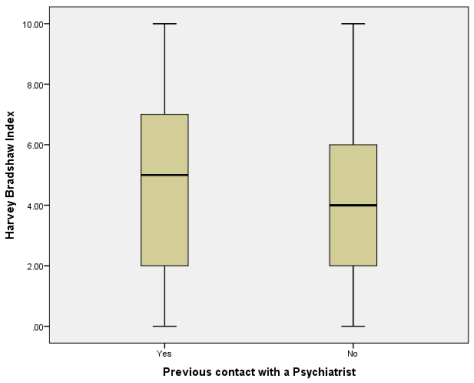












6.2.2.2 Ulcerative Colitis

Disease phenotype will be described by several factors. These are; age at which the subject was diagnosed with the disease, duration of illness in years and whether there is a family history of Crohn's Disease. The second component of the phenotyping will relate to the site of disease at diagnosis and follow up and the Montreal Classification of the disease at diagnosis and follow up.

The psychiatric phenotype will be defined in three ways. Firstly, the present level of affective disorder symptoms as measured by the HADS. Secondly the past psychiatric history and thirdly by the reported use of psychiatric/psychological therapies.

The psychiatric phenotype will then be correlated with the surgical history of the subjects. Finally, the psychiatric phenotype will be compared with the present inflammatory markers; White Cell Count, Erythrocyte Sedimentation Rate, C-Reactive Protein and Haemoglobin. These will all be correlated with the present gastroenterological symptoms of the subjects as measured by the Colitis Activity Index

6.2.2.2.1 Ulcerative Colitis features and psychiatric phenotype

6.2.2.2.1.1 The first table below shows Colitis phenotype and present affective symptoms as measured by HADS.

Disease Phenotype Variable	Statistical Test	Number of Subjects	HADS Anxiety Significance (P)	HADS Depression Significance (P)
Age at Diagnosis	*Pearson Correlation*	121	0.016	0.959
Duration of years of illness	*Pearson Correlation*	121	0.986	0.436
Family History of IBD	*Independent T-test*	121	0.410	0.583
Classification of Illness at Diagnosis (Montreal)	*One-way ANOVAs*	121	0.268	0.064
Classification of Illness at Follow Up (Montreal)	*One-way ANOVAs*	121	0.038	0.296

6.2.2.2.1.2 The following table compares gastrointestinal phenotype with past psychiatric history.

Disease Phenotype Variable	Number of subjects	Does the Subject have a Past History of					
		Depression	Anxiety	Antidepressants	Anti Anxiety	Psychological therapy	Psychiatrist
Age at Diagnosis	121	0.415	0.343	0.676	0.676	0.445	0.501
Duration of years of illness	121	0.712	0.256	0.957	0.957	0.243	0.426
Family History of IBD	121	0.505	0.615	0.275	0.699	0.334	0.245

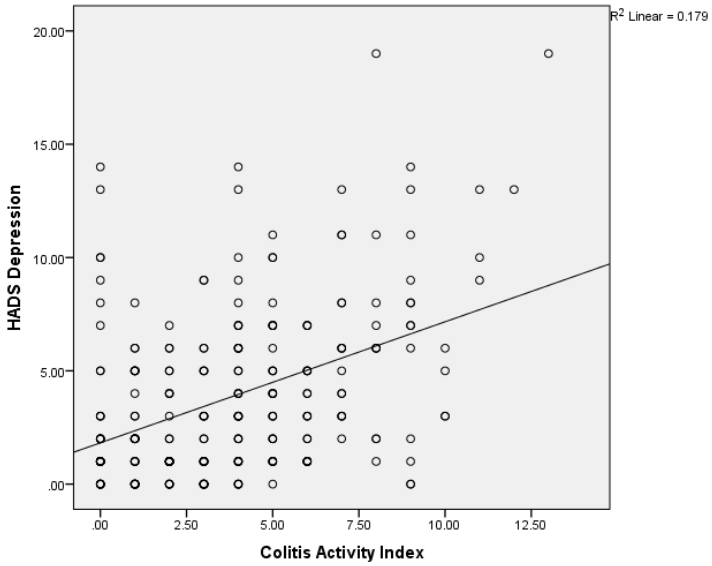
6.2.2.2.1.3 The following chart shows how surgical history may predict psychiatric phenotype. All figures are “p” values.

Procedure	HADS Anxiety	HADS Depression	Anxiety	Depression	Anti Anxiety Medication	Anti depressant	Psychological Therapy
Colectomy	0.175	**0.030**	0.453	0.525	0.085	0.231	0.837
Ileo-Anal Pouch	0.521	0.136	0.545	0.422	0.165	0.202	0.510
Pouchitis	0.767	0.310	0.913	0.692	0.508	0.933	0.522
Tonsillectomy	0.452	0.251	0.791	0.899	0.510	0.759	0.277
Appendectomy	0.222	0.166	0.545	0.942	0.165	0.733	0.429
Joint Problems	0.384	0.268	0.171	**0.044**	0.267	0.334	0.169

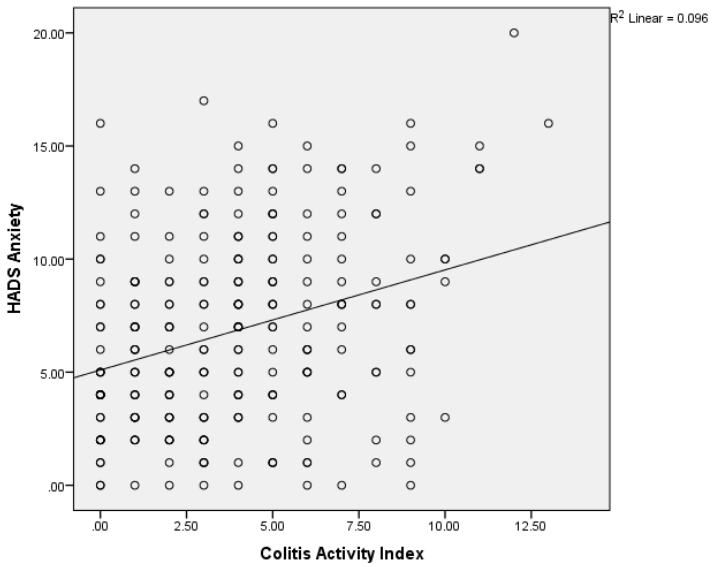
6.2.2.2.2 Symptoms and inflammatory markers as predictors of psychiatric phenotype in UC

The following section looks at the relationship between gastrointestinal symptom scores on the Colitis activity index, psychiatric phenotype on the HADS and inflammatory markers.

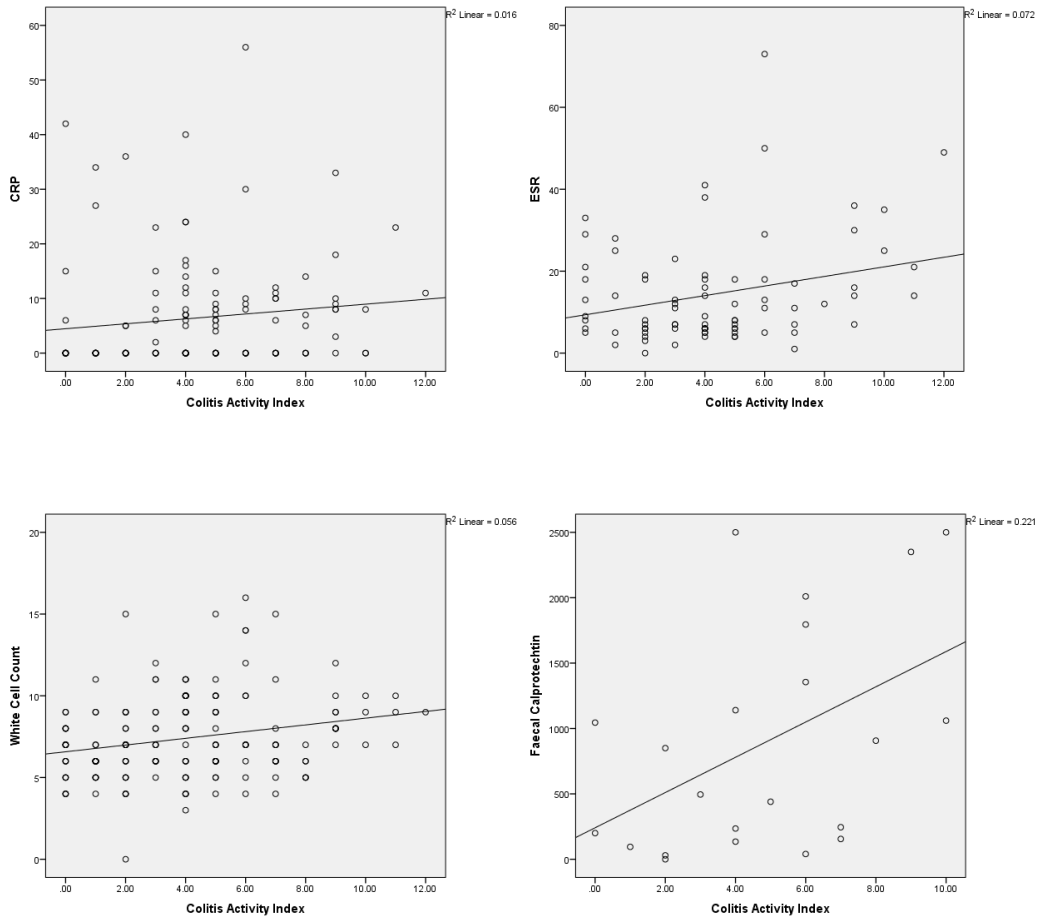
6.2.2.2.2.1 Below is a graph showing the relationship between CAI and HADS Depression



Below is a graph showing the relationship between CAI and HADS anxiety

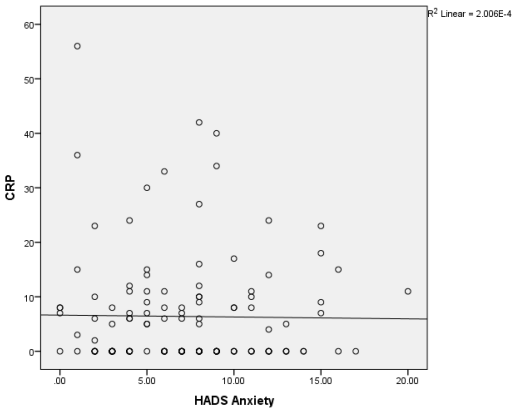


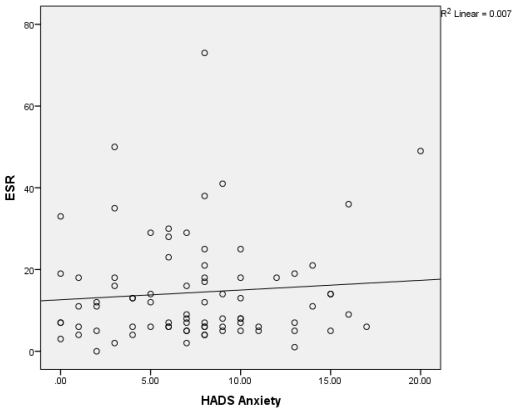
6.2.2.2.2.2 The following section shows the relationship between Colitis activity index and inflammatory markers; CRP, ESR, White Cell Count, Faecal Calprotectin and Haemoglobin.

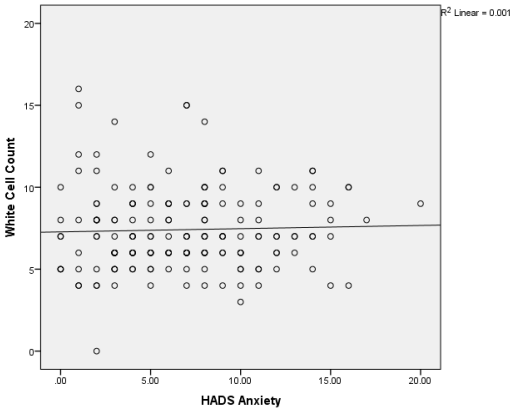


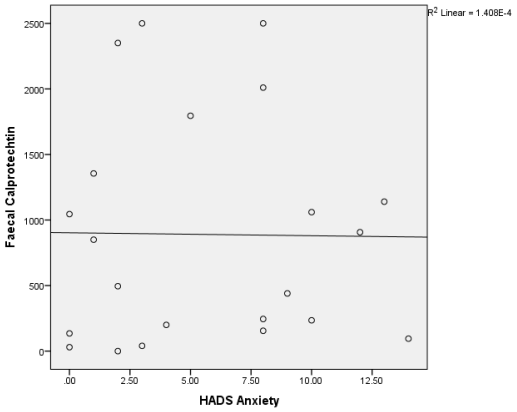
Colitis Activity Index	CRP	ESR	White Cell Count	Faecal Calprotectin
Pearson Correlation	0.127	0.268*	0.237**	0.470*
Sig. (2-tailed)	0.151	0.016	0.002	0.027
N	130	80	173	22

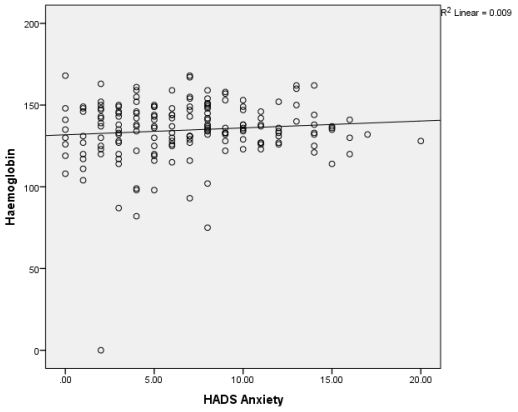
6.2.2.2.2.3 The following section looks at the relationship between HADS Anxiety and inflammatory markers.





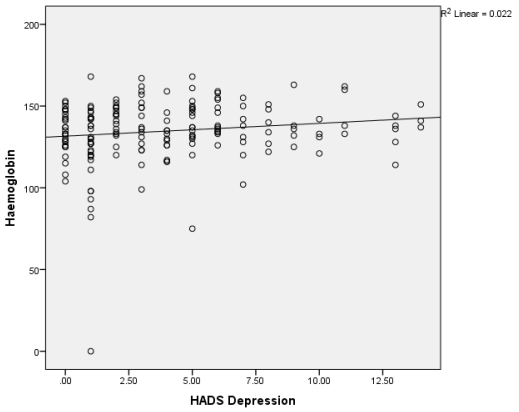


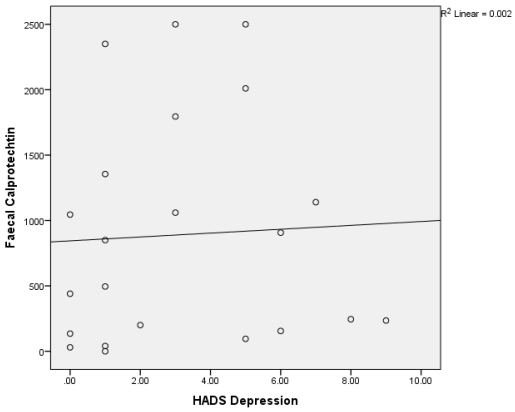


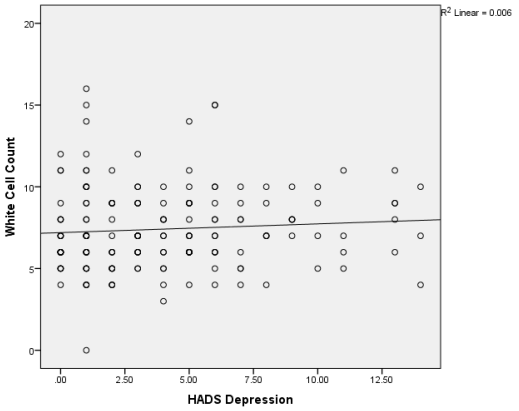


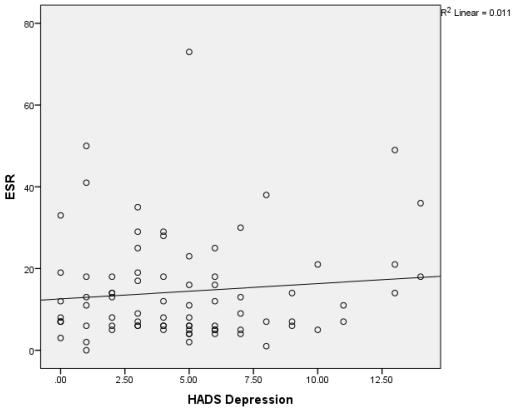
	CRP	ESR	WCC	Faecal Calprotectin	Haemoglobin
Pearson Correlation	-0.014	0.084	0.033	-0.012	0.096
Significance	0.873	0.460	0.662	0.958	0.207
Number	130	80	173	22	174

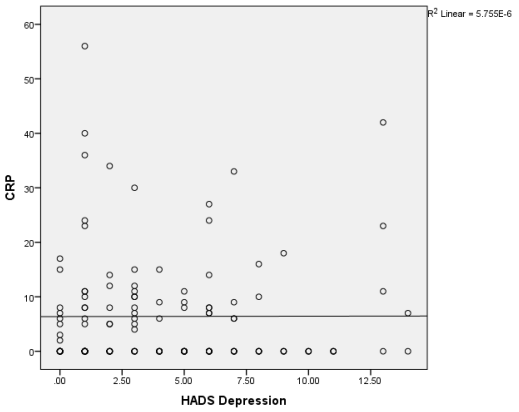
6.2.2.2.2.4 The following section looks at the relationship between HADS depression and Inflammatory Markers.





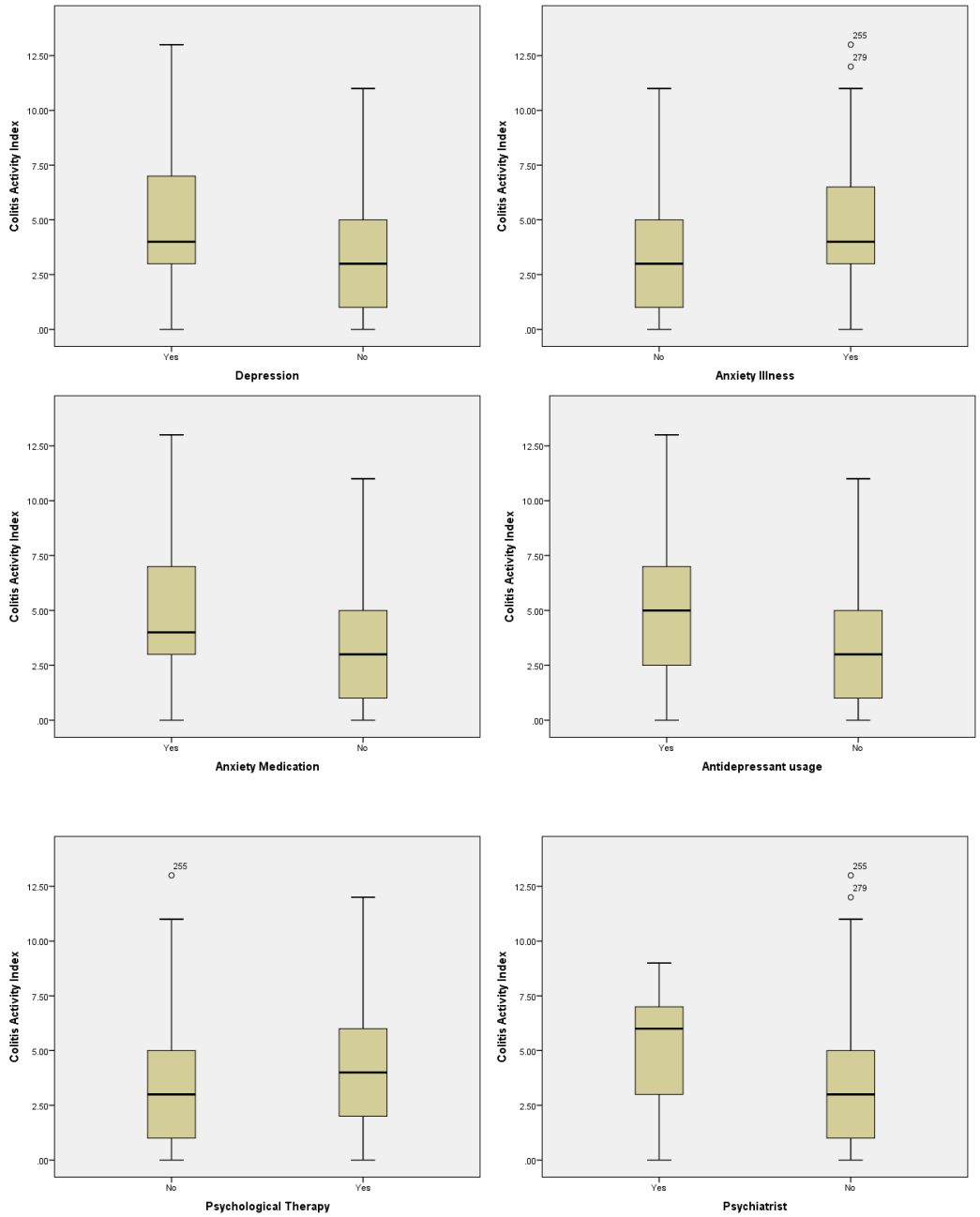






	CRP	ESR	WCC	Faecal Calprotectin	Haemoglobin
Pearson Correlation	0.002	0.104	0.076	0.049	0.149
Significance	0.978	0.357	0.320	0.829	0.050
Number	130	80	173	22	174

6.2.2.2.2.5 The following section compares past psychiatric history with present Gastrointestinal symptoms in patients with UC.



6.2.3 Medication Predictors of Affective disorder

The following section of the results looks at univariate analysis of the effect of specific medications on current affective symptoms. Table below compares patients who are/are not taking each of the medications and their score on HADS anxiety and HADS depression. Many patients will be on more than one medication; as the number of permutations of different medication regimens is high, analysis will be performed on simple comparison of those who are/are not on one of each group. As HADS scores are normally distributed, independent T test is used and results are expressed as F and p values.

	Corticosteroids (Prednisolone, Budesonide)	Aminosalicylates (Mesalazine, Asacol, Pentasa, Balsalazide)	Azathioprine	Mercaptopurine	Methotrexate	Anti TNF immunoglobulins (Adulimamab)
Number of Patients	105	271	139	35	12	25
HADS-Depression	F=4.998 **P=0.026**	F=0.79 P=0.77	F=0.246 P=0.240	F=1.506 P=0.220	F=2.401 P=0.120	F=-13.026 **P<0.001**
HADS - Anxiety	F=0.001 p=0.97	F=0.453 P=0.501	F=0.442 P=0.591	F=0.174 P=0.677	F=1.650 P=0.196	F=-5.565 **P=0.020**

Here it can be seen that those on a corticosteroid medication (either prednisolone or budesonide) are have significantly higher scores on the HADS depression but not anxiety. Subjects on Anti TNF immunoglobulin, Adalimumab score significantly lower on both HADS anxiety and HADS depression scales.

6.2.3.1 Corticosteroid medication

As it has been suggested that the depressogenic effects of corticosteroid medication are a consequence of long-term use, below are three results detailing the effects of this.

In terms of prescription of Prednisolone in the last year (but not now), 113 patients have been compared with 465 who have not been taking this medication. The 85 patients who presently take prednisolone are then compared with those who do not in terms of their current dose and duration of their prednisolone. Dose is based on self-report of daily dose.

	Prednisolone in Last year		Significance (Independent T test)	Duration of Prednisolone (1-32weeks)	Dose of Prednisolone 1-50mg (mg)
Number of Patients	Yes: 113	No: 465		N=85	N=85
HADS Depression (mean)	4.86	3.97	P=0.029	Pearson correlation p<0.001	Pearson Correlation P=0.884
HADS Anxiety (mean)	7.64	6.83	P=0.075	Pearson correlation p=0.025	Pearson correlation p=0.161

Here it can be seen that those patients who have been on prednisolone in the last year have significantly higher depression scores than those who have not. Secondly it can be seen that the duration of prednisolone prescription is significantly correlated with both HADS Anxiety and Depression scores. Thirdly it can be seen that dose of prednisolone does not correlate with either HADS anxiety nor depression.

6.2.4.2 Relationship between prednisolone and the Altman Self Rated Mania Scale (ARSM).

	Prednisolone Now		Significance (Independent T test)	Prednisolone in Last year		Significance (Independent T test)	Duration of Prednisolone (weeks)	Dose of Prednisolone (mg)
Number of Patients	Yes:85	No:493	P=0.172	Yes:112	No:465	P=0.501	N=85	N=85
ASRM (mean score)	3.15	3.73		3.87	3.61		Pearson Correlation P=0.350	Pearson Correlation P=0.03

There appears to be no significant difference between those who are presently on or have been on prednisolone in the last year in terms of their ASRM score. The duration of prednisolone appears to have no effect on the ARSM score but the dose is positively correlated with this.

6.3 Socio demographic predictors of gastrointestinal phenotype

The following section of results will look at how socio demographic factors can predict aspects of the phenotype of inflammatory bowel disease.

Here basic demographic factors will include gender, age, social class, employment status, alcohol usage, income capacity benefit status.

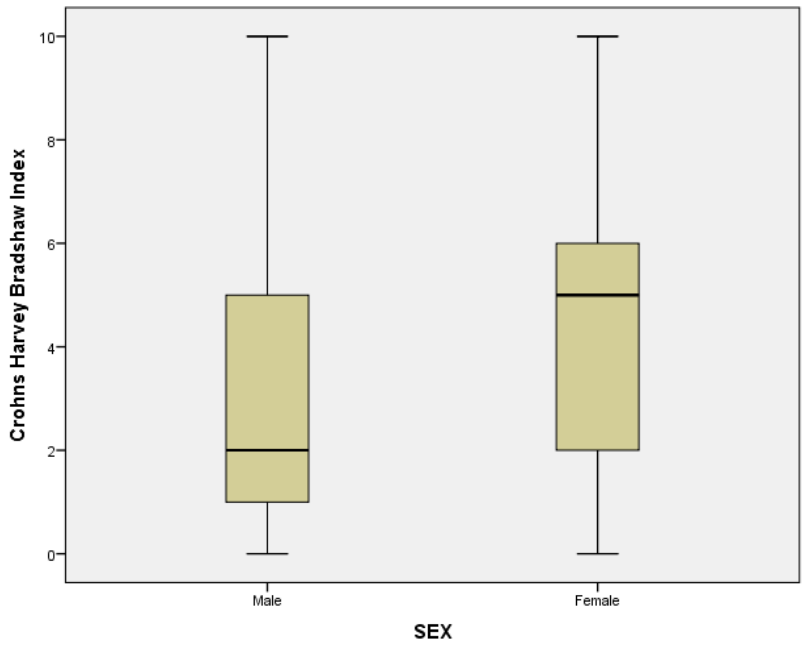
The phenotype of inflammatory bowel disease will be represented by symptom scores on the HBI and CAI, inflammatory markers, past phenotype and past surgical history.

This will be described separately in Crohn's disease and Ulcerative Colitis.

6.3.1 Crohn's disease

This section will look at how GI symptoms are reported by HBI in relation to demographic factors.

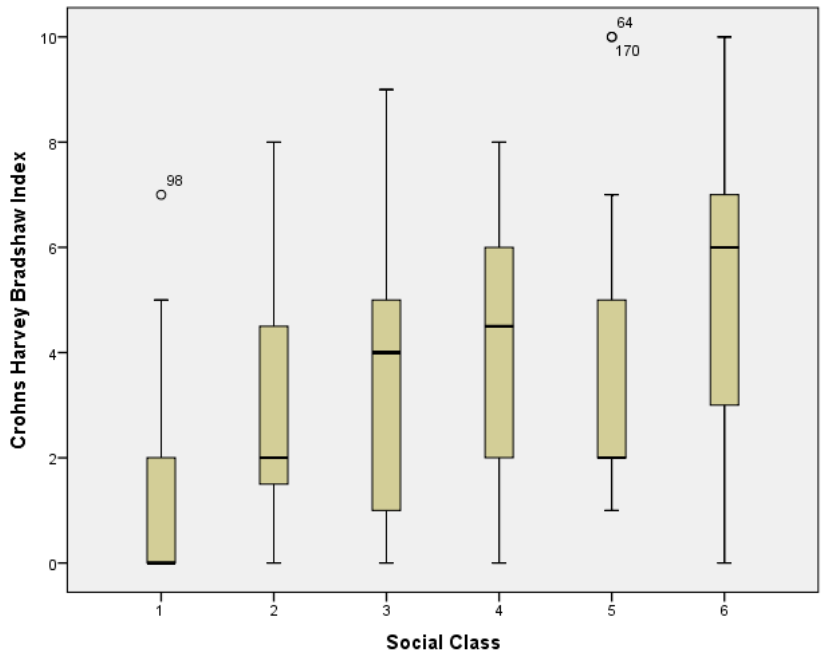
6.3.1.1 Gender and gastrointestinal phenotype



	Number males/total	t	df	Significance (P value)
Crohn's Harvey Bradshaw Index	60/171	-2.703	169	**0.008**
CRP	52/144	-.343	142	0.732
ESR	43/106	-1.604	104	0.112
WCC	59/167	-1.664	162	0.098
Faecal Calprotectin	23/65	-.622	63	0.536
Haemoglobin	59/165	.375	165	0.708

Here it can be seen that gender predicts symptom scores but no difference in inflammatory markers

6.3.1.2 Social Class and gastrointestinal phenotype

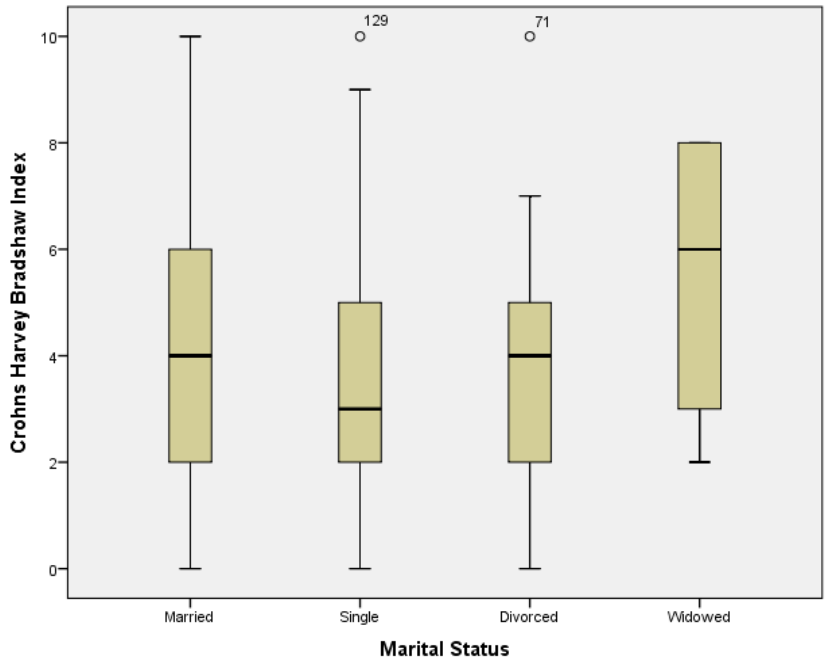


The following chart shows one-way ANOVA for social class and symptom scores and inflammatory markers. Symptom scores on the HBI are significantly correlated with decreasing social class but inflammatory markers are not.

	F	Sig.
Crohn's Harvey Bradshaw Index	4.396	**0.001**
CRP	1.163	0.332
ESR	0.781	0.566
White Cell Count	1.236	0.296
Faecal Calprotectin	2.002	0.095
Haemoglobin	.947	0.453

6.3.1.3 Marital Status

The following shows how marital status relates to HBI symptoms and levels of inflammation

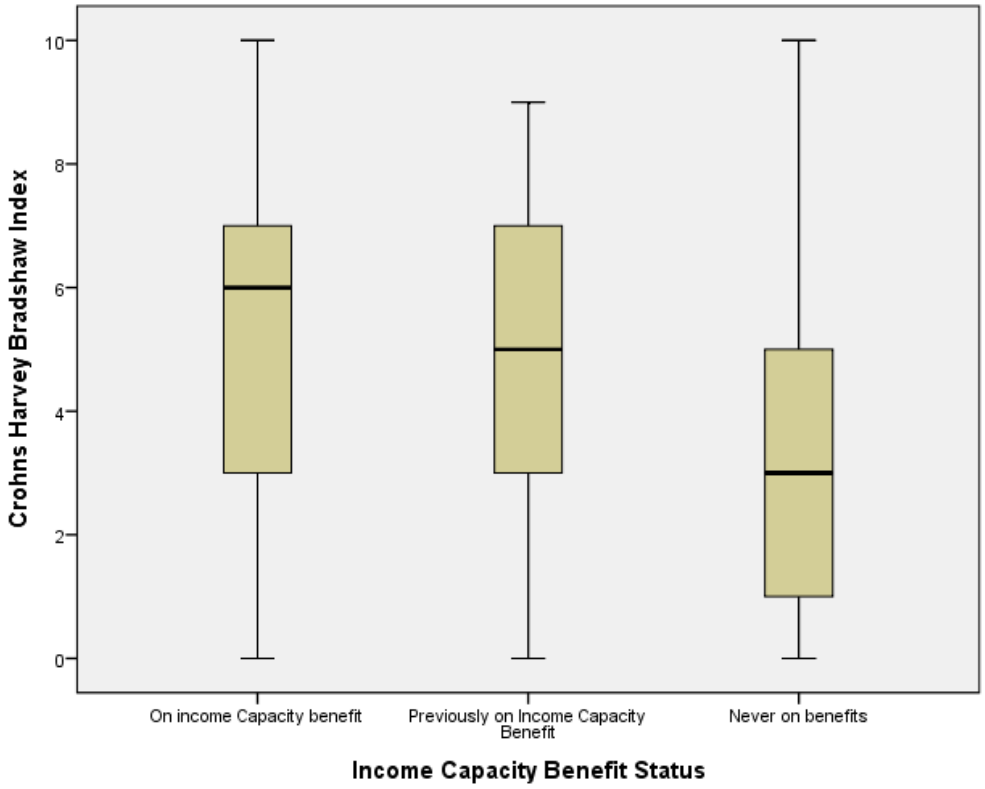


Below is a chart of a one-way ANOVA showing that neither HBI nor inflammatory markers relate to marital status.

	F	Sig.
Crohn's Harvey Bradshaw Index	1.090	0.355
CRP	1.475	0.224
ESR	0.134	0.940
White Cell Count	0.408	0.778
Faecal Calprotectin	0.521	0.669
Haemoglobin	0.572	0.634

6.3.1.4 Incapacity Benefit

The following shows incapacity benefit by symptom scores and inflammatory markers

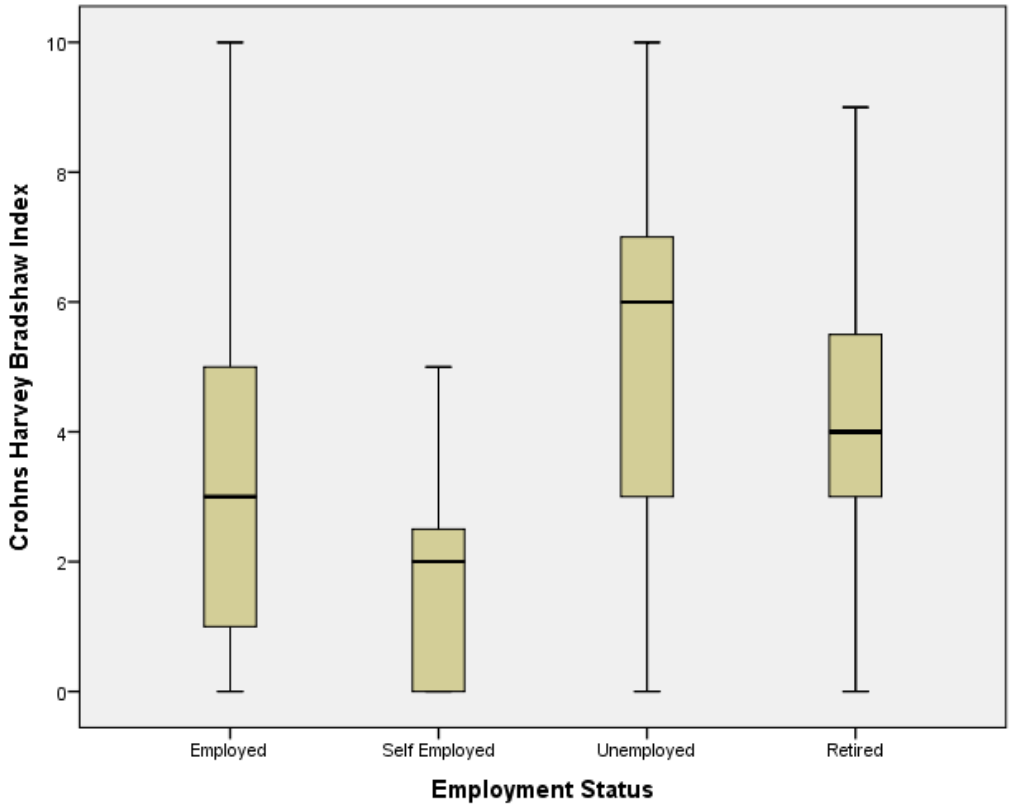


The following chart of one-way ANOVA shows that HBI significantly associates with ICB status.

	F	Sig.
Crohn's Harvey Bradshaw Index	8.108	**<0.0001**
CRP	3.662	0.028
ESR	0.320	0.727
White Cell Count	0.987	0.375
Faecal Calprotectin	0.454	0.637
Haemoglobin	0.773	0.464

6.3.1.5 Employment status

Below are data relating to employment status and symptom scores.



The following chart shows that HBI correlates strongly with Employment status, but inflammatory markers do not.

	F	Sig.
Crohn's Harvey Bradshaw Index	7.337	**<0.0001**
CRP	1.978	0.120
ESR	0.101	0.959
White Cell Count	1.849	0.141
Faecal Calprotectin	0.904	0.444
Haemoglobin	2.548	0.058

6.3.1.6 Age

The following chart shows Pearson correlation between age and HBI and inflammatory markers. It shows that there are no significant relationships between Age and any of these indices.

	Crohn's Harvey Bradshaw Index	CRP	ESR	WCC	Faecal Calprotectin	Haemoglobin
Pearson Correlation	0.102	-0.075	-0.041	-0.014	-0.065	-0.045
Sig. (2-tailed)	0.186	0.370	0.676	0.856	0.607	0.564
N	171	144	106	164	65	167

6.3.1.7 Smoking

The table below compares smokers with non-smokers in terms of scores on HBI and Inflammatory markers. There are no significant differences between groups.

	T	df	Significance (P)
Crohn's Harvey Bradshaw Index	-1.704	169	0.090
CRP	1.041	142	0.300
ESR	-.243	104	0.808
WCC	-1.148	162	0.253
Faecal Calprotectin	.870	63	0.388
Haemoglobin	.433	165	0.666

6.3.1.8 Alcohol Consumption

The following table compares subjects who drink alcohol with those who do not in terms of HBI and inflammatory markers. There are no significant differences between groups on any of these measures.

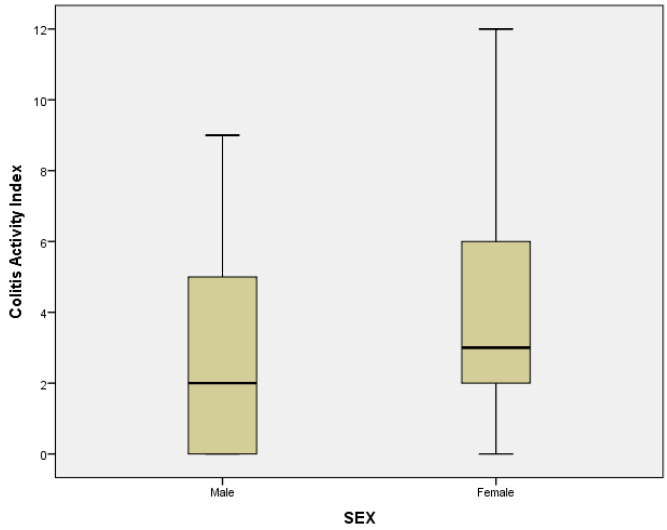
	T	df	Significance
Crohn's Harvey Bradshaw Index	1.696	169	0.092
CRP	.393	142	0.695
ESR	.276	104	0.783
WCC	-.093	162	0.926
Faecal Calprotectin	-1.480	63	0.144
Haemoglobin	-.954	165	0.342

6.3.2 Ulcerative Colitis

The following section shows sociodemographic predictors of symptoms and inflammatory markers for patients with ulcerative colitis.

6.3.2.1 Gender

Disease Factor	t	df	Sig. (2-tailed)
Colitis Activity Index	-2.514	117	0.013
	-2.609	116.089	0.010
CRP	.068	89	0.946
	.068	88.535	0.946
ESR	-1.629	74	0.108
	-1.683	73.969	0.097
WCC	-1.510	116	0.134
	-1.484	96.744	0.141
Faecal Calprotectin	-1.232	36	0.226
	-1.373	20.000	0.185
Haemoglobin	-.516	116	0.607
	-.494	86.155	0.622



From the above it can be seen that females have significantly higher on the Colitis Activity Index but there are no significant differences on any of the inflammatory measures.

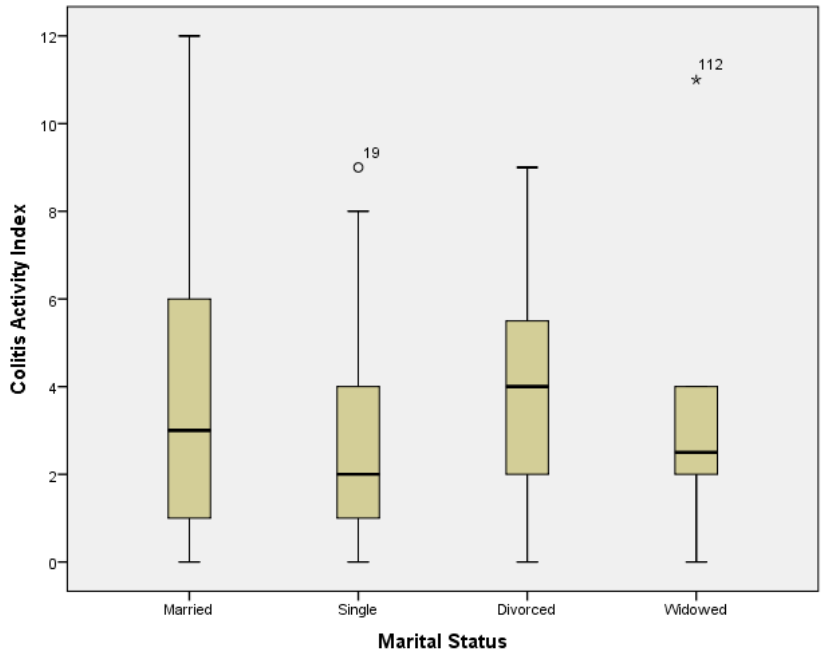
6.3.2.2 Age

Below is a Pearson correlation between age and CAI and Inflammatory markers. There are no significant correlations.

	Colitis Activity Index	CRP	ESR	WCC	Faecal Calprotectin	Haemoglobin
Pearson	-.040	.153	.177	.090	-.096	.114
Significance	0.665	0.148	0.126	0.332	0.568	0.219
number	119	91	76	118	38	118

6.3.2.3 Marital status

Below is a boxplot and chart showing the association between marital status and symptom reporting on the CAI. There are no significant associations.

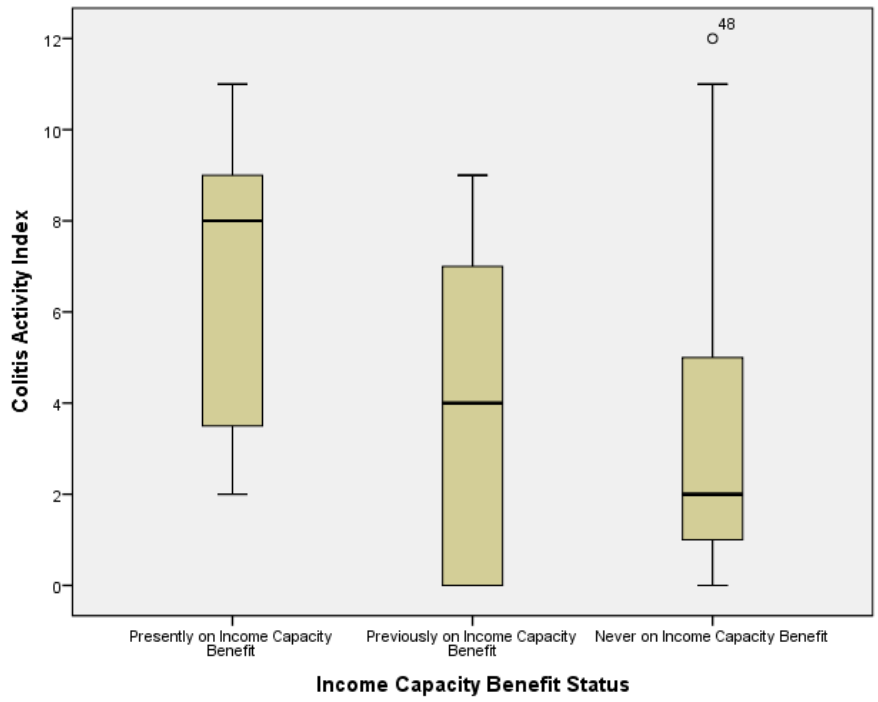


	F	Sig.
Colitis Activity Index	0.776	0.510
CRP	0.502	0.682
ESR	1.373	0.258
WCC	1.190	0.317
Faecal Calprotectin	0.382	0.767
Haemoglobin	0.672	0.571

6.3.2.4 Incapacity Benefit

Below can be seen the correlations between Incapacity Benefit and CAI and Inflammatory markers. Here ICB is correlated with CAI and CRP.

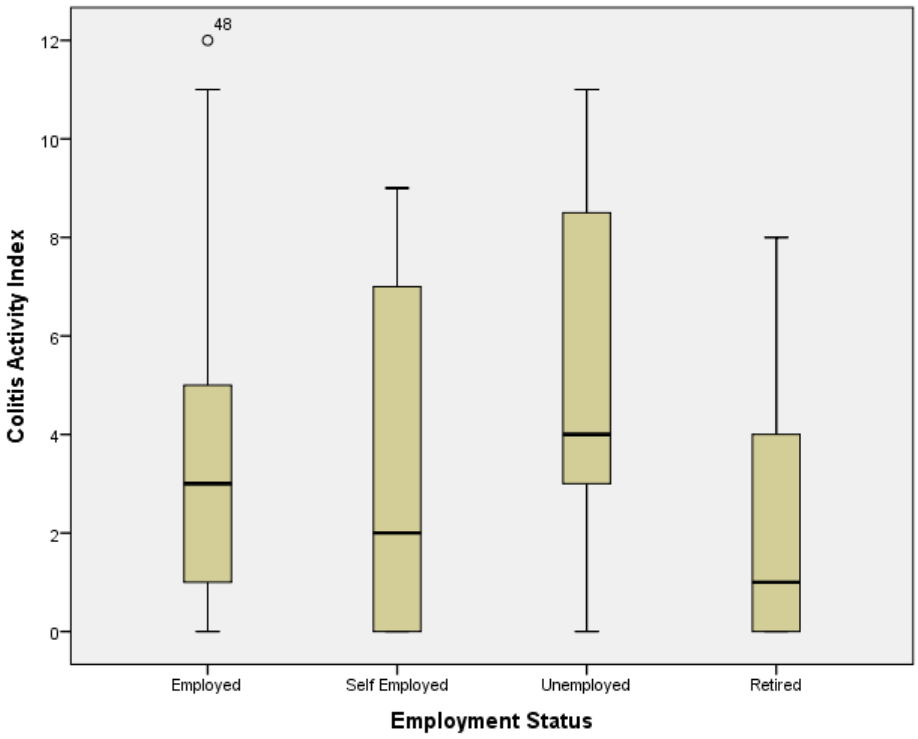
	F	Sig.
Colitis Activity Index	5.374	**0.006**
CRP	3.316	0.041
ESR	0.818	0.446
WCC	1.156	0.319
Faecal Calprotectin	0.234	0.632
Haemoglobin	2.033	0.136



6.3.2.5 Employment status

Below is shown the correlation between employment status and CAI/Inflammatory Markers. There are no significant associations to be seen.

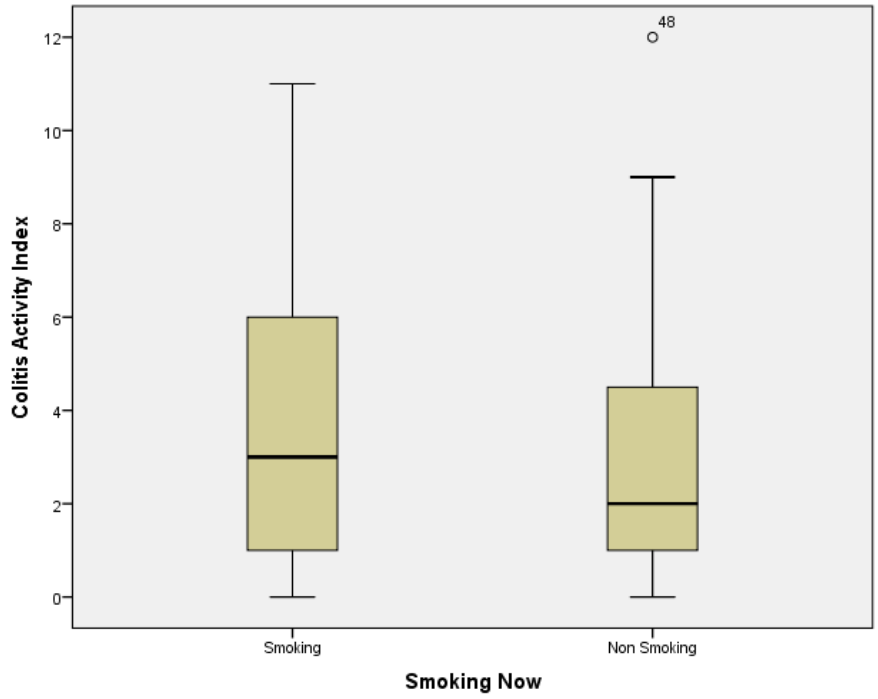
	F	Sig.
Colitis Activity Index	1.851	0.142
CRP	.054	0.983
ESR	.179	0.911
WCC	1.617	0.189
Faecal Calprotectin	.967	0.419
Haemoglobin	1.965	0.123



6.3.2.6 Smoking

Below is correlation between Smoking, CAI and inflammatory markers. There are no significant associations.

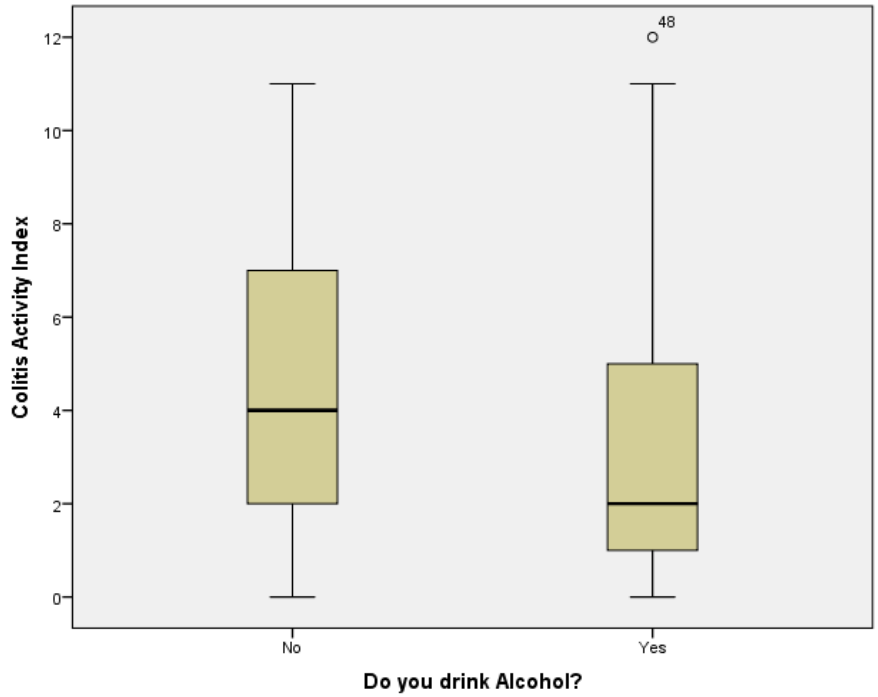
	t-test for Equality of Means		
	t	df	Sig. (2-tailed)
Colitis Activity Index	-1.132	117	.260
CRP	-1.220	89	.226
ESR	-1.397	74	.167
WCC	-1.744	116	.084
Faecal Calprotectin	-.863	36	.394
Haemoglobin	-1.427	116	.156



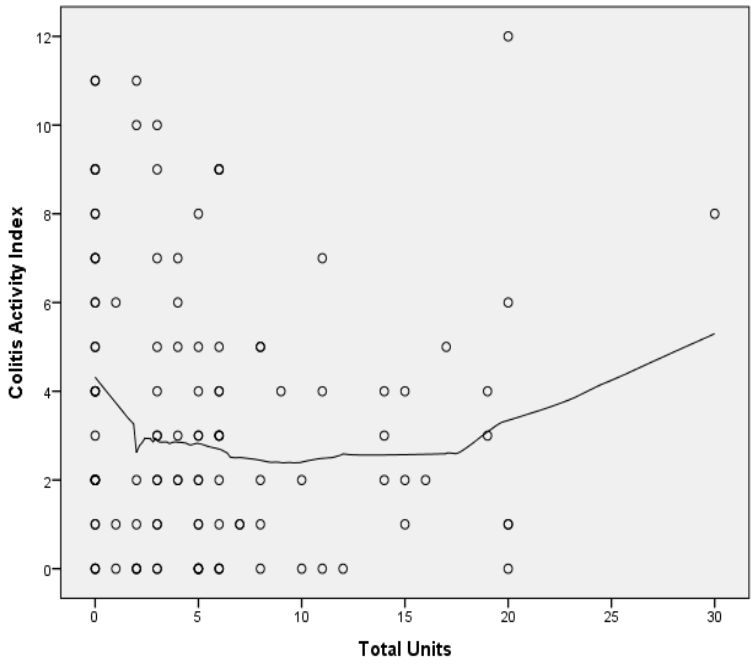
6.3.2.7 Alcohol consumption

Below are the correlations between alcohol consumption and CAI/Inflammatory markers. Drinking alcohol is correlated with higher CAI but not inflammatory markers.

	t-test for Equality of Means		
	t	df	Sig. (2-tailed)
Colitis Activity Index	-2.343	117	0.021
CRP	-1.692	89	0.094
ESR	-.372	74	0.711
WCC	.290	116	0.772
Faecal Calprotectin	.659	36	0.514
Haemoglobin	.741	116	0.460



Below is a scatter plot showing units of alcohol against CAI. There appears some suggestion of a “J” shaped relationship in which those who do not drink and those who drink excessively both score higher on CAI.



6.4 Multivariate Analysis

The following section of the results will be the multivariate analysis. Multivariate linear regression analysis was used to identify the most important independent predictors of HADS anxiety and depression. All significant predictors were entered into the regression model for Crohn's Disease or Ulcerative Colitis and HADS Anxiety or Depression. A forward stepwise model was then used to assess significance of independent variables.

Dependant Variable	Entered variables	Independent variables	R^2	Significance (P value)
Crohn's Disease HADS Anxiety			0.239	
	Harvey Bradshaw Index, CRP, ESR, WCC, Prednisolone now, Prednisolone in last year, Gender, Marital Status, Household composition, Smoking, Alcohol, Employment status, Incapacity Benefit Status, Disease duration, Disease Site, Vienna Classification, Disease onset	Harvey Bradshaw Index		0.02
		Incapacity Benefit Status		<0.001
		Employment Status		0.023
Crohn's Disease HADS Depression			0.290	
		Harvey Bradshaw Index		0.02
		Incapacity Benefit Status		<0.001
		Employment Status		0.039
Ulcerative Colitis HADS Anxiety			0.372	
	Simple Colitis Activity Index, CRP, ESR, WCC, Prednisolone now, Prednisolone in last year, Gender, Marital Status, Household composition, Smoking, Alcohol, Employment status, Incapacity Benefit Status, Disease duration, Disease Site, Vienna Classification, Disease onset	Incapacity Benefit Status		<0.001
		Prednisolone in Last year		0.015
		Simple Colitis Activity Index		>0.001
Ulcerative Colitis HADS Depression			0.384	
		Incapacity Benefit Status		<0.001
		Prednisolone in Last year		0.048
		Gender		0.036

Here it can be seen that Gender, Incapacity benefit status, employment status, prednisolone in the last year and physical symptom indices represent independent predictors of Anxiety and Depression in this population.

Below is multivariate analysis for predictors of physical symptoms: Harvey Bradshaw Index for Crohn's Disease and Colitis Activity Index for Ulcerative Colitis. A forward stepwise model was then used to assess significance of independent variables.

Dependant Variable	Entered variables	Independent variables	R^2	Significance (P value)
Crohn's Disease Harvey Bradshaw Index			0.322	
	HADS Depression & Anxiety, CRP, ESR, WCC, Prednisolone now, Prednisolone in last year, Gender, Marital Status, Household composition, Smoking, Alcohol, Employment status, Incapacity Benefit Status, Disease duration, Disease Site, Vienna Classification, Disease onset	HADS Depression		<0.001
		Gender		0.018
		WCC		<0.001
Ulcerative Colitis Colitis Activity Index			0.172	
	HADS Depression & Anxiety, WCC, CRP, ESR, WCC, Gender, Marital Status, Household composition, Smoking, Alcohol, Employment status, Incapacity Benefit Status, Disease duration, Disease Site, Vienna Classification, Disease onset	HADS Depression		<0.001
		Gender		0.016
		WCC		0.003

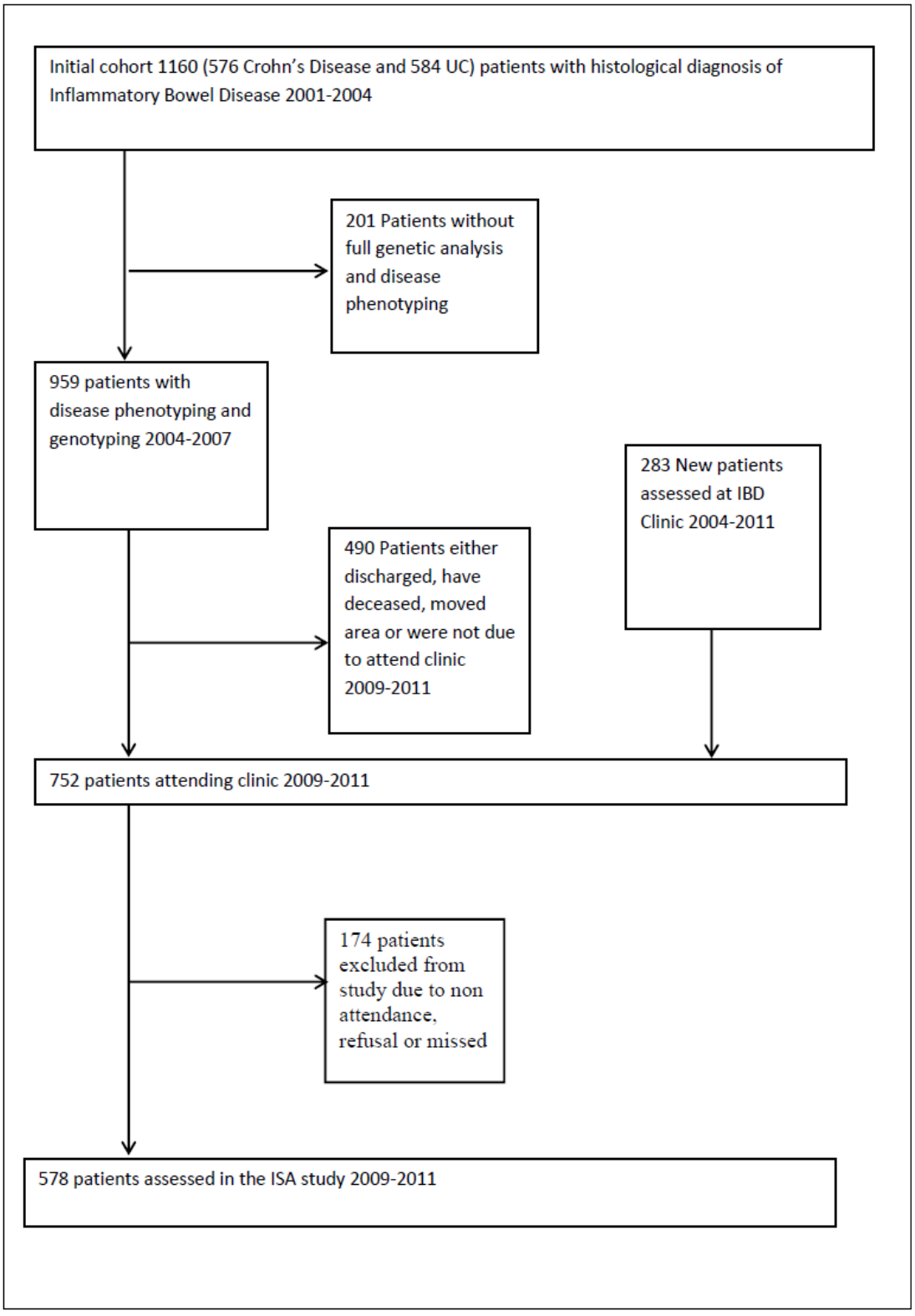
These results show that higher levels of reported physical symptoms are predicted by Gender, WCC and HADS Depression.

7.0. Discussion

The discussion for this thesis will be divided into four main sections. These will be a description and discussion of the main results, critique of the methodology, implications of the work and discussion on future research.

7.1 Main results

In total 655 patients were recruited to the ISA study of whom 254 had Ulcerative Colitis, 323 had Crohn's Disease and 78 had Coeliac disease. Of 752 patients attending the outpatient IBD clinic during the study, 578 (76.8%) were recruited. Of the IBD sample 293/578 (50.6%), were part of the original IBD cohort assessed between 2001-2004. Below is a flowchart outlining the recruitment into the study.


Initial cohort 1160 (576 Crohn's Disease and 584 UC) patients with histological diagnosis of Inflammatory Bowel Disease 2001-2004
201 Patients without full genetic analysis and disease phenotyping
959 patients with disease phenotyping and genotyping 2004-2007
283 New patients assessed at IBD Clinic 2004-2011
490 Patients either discharged, have deceased, moved area or were not due to attend clinic 2009-2011
752 patients attending clinic 2009-2011
174 patients excluded from study due to non attendance, refusal or missed
578 patients assessed in the ISA study 2009-2011

The subjects recruited into the ISA study were compared to those recruited into the original sample. Below is a table showing a comparison of these groups which shows that there are no significant differences between them other than age.

Variable	Original sample not included in ISA	ISA sample	Statistical significance
Year of birth	1958.85	1966.62	P=0.001 Independent T test
Gender	37.9% male	35.3% male	P=0.535 Mann Whitney U
Age at Diagnosis	33.4yrs	31.7yrs	P=0.343 Independent T test
Family History Positive	22.1%	24.2%	P=0.647 Independent T test
Vienna Classification of illness at diagnosis			P=0.312 Mann Whitney U
Number of Surgical procedures	0.86	0.94	P=0.444 Independent T test
Smoking status	22.2% presently smoking	23.9% presently smoking	P=0.132

7.1.1 Socio Demographic Characteristics of IBD and Coeliac Patients

Consistent with the epidemiology of IBD, the ISA cohort show a female preponderance (57.1%). However, when comparing Crohn's Disease patients with UC and Coeliac disease with regards to other demographic variables many differences exist. Crohn's patients are younger. Nearly half (48.8%) are martially single unlike UC (29%) and Coeliac Disease (34%). Crohn's disease patients are also twice as likely to live with their parents. In other studies, 55% of patients at diagnosis were married and 30% were single. (232)

With regards to employment status, some 19% of Crohn's Disease patients are unemployed compared to 10-11% UC and Coeliac disease. Furthermore 25% of Crohn's Disease patients have been on ICB compared with 12% Coeliac and 16% UC. In other studies, when compared with the general population, patients with IBD were more likely to be unemployed. (232) Crohn's disease appeared to affect employment more than ulcerative colitis. Here around 10% of those with Crohn's were unemployed at the time of diagnosis compared with 6% of UC. (232) This shows that the ISA population were different to other populations.

In summary, Crohn's disease patients are more likely to be unemployed, on ICB and living with parents than the other two groups. Some of these differences may be accounted for by age, but the increased use of ICB suggests that Crohn's patients will have a far more socially and occupationally disabling illness.

7.1.2 Disease Characteristics

In terms of disease characteristics, 43% of patients with Crohn's disease are diagnosed between the ages of 20 and 29. The mean age of diagnosis is 27.1 years. In a meta-analysis, incidence rates for both CD and UC were highest among the second to the fourth decade of life. Therefore, IBD affects individuals in the most formidable and productive years of life, resulting in long-term cost to the patient, health care system, and society. (233)

Twenty three percent of patients with Crohn's Disease have a family history of the illness. The rates of familial IBD in probands ranges between 1.25% and 20% in other studies. (234)

At diagnosis, patients present with disease in the Ilium (57%) and Colon (46.5%). These areas remain as the principally diseased areas. The prevalence of anal and rectal disease increases as the disease progresses. From other studies, at the time of diagnosis, 35-45 % had pure ileitis, 36-40 % had colitis alone, and 29-35 % had ileocolitis. (235)

According to Vienna classification, the most common type of disease in this group is A2L1B1. Just 9% of patients are given an Ileal stoma for treatment of their disease. Fifty-six percent of patients have a bowel operation; 3.5% of patients have more than 3 operations. From systematic review of outcome in IBD, approximately half of the patients require surgery 10 years after diagnosis. (235) This suggests that the patient group used in the ISA study may be representative in terms of their IBD.

In Ulcerative colitis the mean age of diagnosis is 32.3 years, and 14.9% of patients have a family history of the illness. The most common site of disease at diagnosis is the hepatic flexure (81.2%). The most common type of disease at diagnosis is E2: Left sided UC (distal UC): Involvement limited to a proportion of the colo-rectum distal to the Splenic flexure. Just 7.5% of patients receive a Colectomy as part of the treatment. These findings are consistent with existent literature on the clinical phenotype of UC. (236)

CRP is presently the most popular marker of measuring disease activity in IBD. Of 180 patients with Crohn's disease 85 (47.2%) had normal CRP and of 130 patients with UC, 72 (55.4%) had a normal CRP. (236) While just 12.5% of patients had a normal Faecal Calprotectin, these were taken from just 56 patients of 315 who had immune markers available and are likely to represent those with more severe illness. This may be a sample bias as those who had this test were likely to be relapsing. It is therefore likely that around half of the patients in the ISA study had increased inflammation and consequently were likely to have active disease. Importantly those who had inflammatory markers in the normal range had all histological diagnoses of IBD. This is important as many population studies of IBD are unable to ensure subjects had prior histological diagnoses.

7.1.3 Psychiatric phenotype

Psychiatric phenotype has been defined by symptom scales, self-reported past psychiatric diagnosis, self-report of prescribed psychiatric medication and contact with a mental health professional.

When considering psychiatric phenotype, there are several similarities and differences between IBD and Coeliac disease group. IBD patients reported the same rate of past psychiatric diagnoses as those with Coeliac. (There were no significant differences with regards to depression, anxiety, panic disorder, OCD and Bipolar illness). This may relate to the fact that patients with Coeliac Disease who presented to outpatient clinics for follow up were a more complex group or required more health service usage.

Of note the rate of Bipolar illness in the IBD cohort is around 1% (6/657) which is what would be expected in community samples. The inclusion of self-reports of psychiatric medication or contact with mental health professionals is a measure of past psychiatric history which may not be accounted for by psychiatric diagnosis alone. Here, Coeliac Disease patients are very similar to IBD patients other than with regards to contact with a psychiatrist where the rate in IBD is twice that of coeliac disease. This may well represent the fact that patients with IBD have more severe psychiatric illness.

There are several important findings with regards to the HADS scores of IBD and Coeliac Disease patients. There are no significant differences between mean scores for the three groups or between each pair of groups with regards to HADS total or HADS anxiety. There exists a significant difference between Crohn's disease and the UC/Coeliac with regards to HADS depression scores. Patients with Crohn's disease have higher depression scores than these other illnesses. There are many reasons which could account for this. As above, patients with Crohn's have higher levels of unemployment and ICB. Patients are also more likely to be unmarried and younger. Patients with Crohn's may have had earlier onset of

illness and have had greater adversity as a consequence. Crohn's disease may simply be a more symptomatic and disabling illness. Crohn's patients have had several surgical procedures compared with UC but surprisingly UC (by this argument) should have higher levels of depression compared with Coeliac disease.

There are no differences between diagnoses with regards to Manic symptoms as measured by the ASRM. This suggests that the likelihood of bipolar affective illness is not mediated by presence of bowel illness.

Of 578 patients with IBD, 148 patients (25.6%) had HADS Depression scores of 7 or over which is suggestive of current depressive illness. This is consistent with findings from other studies in chapter 3 in which rates of depression ranged from 22-62% in IBD outpatients. Of the 148 patients, 87 (58.7%) had never received either an antidepressant or any psychological intervention in the past. (Eighty-six, {58.1%} had never received any psychological intervention and 72 {48.6%} had never received an antidepressant).
This finding suggests that around 15% of patients attending a GI outpatient clinic suffer from a depressive illness and are currently not receiving any treatment.

This contrasts with 185 patients with IBD who report a past history of depression. Of these patients, 155 (83.8%) have received an intervention. Those who have not received an intervention would be subjects who have erroneously reported depressive illness, those who had such a mild illness as to not warrant an intervention and those who refused or failed to comply with an intervention. As 83% of those who reported having depression received an intervention, it would suggest that the self-reporting in this instance may be

quite accurate. Furthermore, it would suggest that when patients attend the local services with depression, most are able to receive an intervention.

Similarly, 330/655 (50.2%) patients report HADS anxiety scores of 7 or above suggestive of anxiety disorder. This is consistent with previous literature which shows that 33-65% of patients with IBD have clinical levels of anxiety as seen in chapter 3. Of 330 patients, just 114 (34.5%) have received either a psychological or pharmacological intervention. This means that 32.9% of patients attending a GI clinic have clinical levels of anxiety and are presently receiving no intervention. This does not mean they have necessarily a diagnosable anxiety disorder such as Generalised Anxiety Disorder – indeed their primary diagnosis may be Major Depressive Disorder as part of which anxiety is a strong feature. Notwithstanding this caveat, there is clearly a high level of untreated (and largely undiagnosed) anxiety symptoms in this population.

These findings represent an unmet need in the out-patient population. Such findings apply for both IBD and Coeliac disease patients.

7.1.4 Medication usage

With regards to medication, 85 (14.9%) patients are presently on prednisolone and 20 (3.5%) were on budesonide. 113 (19.6%) were on prednisolone and 5 (1.0%) were on budesonide in the last year but no longer are. The range of prescription duration is likely to

represent several different clinical situations. Amongst these patients there will be those experiencing acute relapse who are likely to be on >20mg for a short period of time. Secondly there are those who are on a low dose of around 1mg for many years who are unable to stop taking this medication. Thirdly there are those who are undergoing a process of reduction of steroids following a resolving relapse. Other studies suggest that half of the patients receive steroids during disease course. (235)

At the time of the study 17 (2.9%) patients were on Infliximab and 25 (4.5%) of patients were on Adalimumab. These anti TNF medications represent a small but significant group of patients who are likely to be suffering from severe disease. The use of Anti TNF medications is reserved for severe cases and usage in this patient group is consistent with national guidelines.

7.1.5 Socio demographic predictors of Affective illness

The first part of the univariate analysis has concentrated on socio demographic predictors of affective illness. When looking solely at the IBD cohort; gender, marital status, smoking, ICB and employment status are significant predictors of anxiety when HADS Anxiety is used as a continuous measure.

Significant predictors of Depression include smoking, alcohol consumption, ICB and Employment Status but not marital status. Household composition appears to have no effect on either depression or anxiety.

Female gender has been consistently associated with higher levels of affective symptoms. Similarly, being married is consistently associated with lower levels of affective symptoms compared with being single, widowed and divorced. The fact that marital status and household composition does not correlate with depression in this study may relate to a ceiling effect i.e. the presence of a disease is a more important modifier in this group. This is consistent with one other study in which marital status does not predict depression in this group (237).

With regards to employment, those employed have lower levels of anxiety and depression. Those who are self-employed have the lowest levels. The direction of causality is unknown here. Are subjects more depressed or anxious because they are unemployed or have co morbid depression or anxiety illness prevented subjects from working? The choice to be self-employed may reflect either flexibility of working pattern leading to less depression/anxiety or a more self-reliant personality which has less tendency to depression/anxiety. ICB is likely to be a secondary index of unemployment. This is again consistent with other literature in which unemployment predicts depression in IBD (237)

Alcohol usage and smoking may relate to affective illness in this study in several ways. High alcohol consumption may precede or follow affective illness. Alternatively, both smoking and alcohol consumption may be indices for low social class and multiple social adversities.

Hence these act as predictors of both affective illness and predictors of IBD. These represent well known sociodemographic associations in literature of depression.

Of note there appears to be a trend for both anxiety and depression with regards to an association with social class. HADS depression and anxiety scores both increase from social class 1 through to social class 6. This is consistent with the body of literature on the social determinants of depression. (237)

In the context of the ISA study the socio demographic predictors of affective illness are important in that, given a high level of depression in the out patient population, social factors may represent target groups which can be screened and treated.

7.1.6 Disease predictors of depression

In considering disease factors which would predict affective illness in this population, it may have been assumed that those with younger onset, longer duration of disease and more surgical procedures would experience more psychiatric illness. The picture presented in the results from this study is however more complicated. In most of the findings relating to severity of disease, depression is the most noticeable psychiatric phenotype whereas anxiety is not.

Age above 18 rather than below appears to predict depression as evidenced by past depression diagnosis, contact with mental health professional and current HADS depression. This finding may relate to a powering effect as only 36 patients with data were diagnosed below the age of 18. Notably those who have been diagnosed above the age of 18 are more likely to have seen a psychiatrist (whereas there are no differences in terms of contact with other mental health professionals). This may suggest that those diagnosed above the age of 18 have more severe depression. This may also relate to the fact that the psychiatric sequelae of medical illness happen later in life. At the time of assessment in this study, early onset patients may not have developed their psychiatric presentations.

Additional interpretations may relate to the fact that age of onset of depression is likely to be later in life or that young people may adapt to their illness at an earlier stage. Subjects diagnosed above the age of 50 may be experiencing other physical illness or have more financial or family responsibilities. As expected, duration of illness remains important and is correlated with depression but not anxiety. Indeed, the older age predictor may simply relate to duration of illness.

There is no relationship between a family history of IBD and present or past psychiatric illness. It has been suggested that those with familial illness may have a more severe phenotype or younger onset. (233) Additionally, from a psychological perspective, witnessing IBD in a parent or other family member may lead to higher levels of distress. There is no evidence of this however from this study. Reasons may relate to a definition of "family history" being any blood relative and therefore negating an environmental and reducing a genetic influence on the subject's illness.

Although only pertaining to a small number of subjects, the presence of oral Crohn's Disease appears to significantly relate to HADS Depression, past history of depression and experience of psychiatric treatments. If this is a true relationship, there could be several explanations for this. Oral illness may be an index of severe disease or indeed a specific clinical subtype. Oral disease itself may be more distressing and disabling in terms of daily activities. As will be discussed later, oral disease may be an index of a possible cerebral pattern of inflammation. Conversely do patients with depression behave differently (for example, they smoke more or have worse dentition) and are more susceptible to oral disease. With either direction of causality, it may be noted that patients presenting with oral disease may well have depression and oral disease could be a useful index for screening. Similarly, there appears to be an association between joint problems in Ulcerative Colitis and depression. There appears to be no previous literature on these findings.

Current HADS depression in Crohn's Disease is significantly associated with having had a bowel resection, the number of bowel resections, having an ileal stoma and the total number of therapeutic surgeries. Similarly having a colectomy is associated with higher HADS in patients with Ulcerative Colitis. This is consistent with other work on depression in IBD where surgery is known to be a predictive factor for depression. (238)

It makes great sense that suffering incurred from severe illness as measured by extensive surgical treatment would be a predictor of current depressive symptomatology. However,

there are several other implications of this finding. Firstly, there is no relationship between HADS anxiety and any surgical history. Why should depression be the predominant psychiatric phenotype? From the time course of the study, the surgical history relates to interventions which have taken place over many years. It is possible that anxiety symptoms relate more to present difficulties rather than past ones.

A second question which may relate to this association is about whether those with a prior depressive illness are more likely to have surgical treatment. Here depression may have led immunologically to a more severe disease. Alternatively, those who suffer from depression are more likely to use health services and have more surgery. It is beyond the scope of this study to be able to demonstrate a temporal association between onset of depression and subsequent need for surgery. However, it is possible, and consistent with literature, that those with depression undergo more surgical procedures as it has been shown that depressed patients have greater healthcare utilisation. (237) Irrespective of the direction of causality, patients who have a significant surgical history represent a high-risk group for depression and a possible target for screening.

7.1.7 Symptom and Inflammatory predictors of affective illness

Thus far the results have focussed on categorical data which relates to current and past affective illness. We have seen that duration of illness and extent of surgical treatment predicts both past and present depressive illness. We will now turn to how contemporaneous levels of inflammation may relate to both affective illness and physical symptoms. There exist three hypotheses for this component of the study. Inflammatory markers CRP, ESR, WCC and Faecal Calprotectin are indicators of disease severity. Concurrently self-reported symptom measures Harvey Bradshaw Index (HBI) for Crohn's Disease and Colitis Activity Index (CAI) for ulcerative colitis are also well validated measures of disease activity. Psychiatric symptoms (HADS) should correlate with severity of disease measured by symptom reports. This may be due to depressive or anxiety symptoms arising due to the presence of physical symptoms (or physical symptoms being more noticeable in the context of a depressive illness). Psychiatric symptoms should also correlate with the level of inflammation, given what has already been discussed about common inflammatory disruption in both depression and IBD such as raised TNF and IL 2,6,10.

In terms of hypotheses; HADS should correlate positively with physical symptom scores and inflammatory markers; physical symptom scores should correlate positively with inflammatory markers.

In patients with Crohn's disease, the results show that HBI correlates with WCC and Faecal Calprotectin but not CRP nor ESR. Similarly, in UC, CAI correlates with ESR, WCC and Faecal

Calprotectin but not CRP. It should be the case that symptom scores correlate with severity of disease. Given the sample size, the lack of correlation is unlikely to be a powering issue. It is therefore curious that this correlation is not very strong. The strongest marker is Faecal Calprotectin which, as a marker of intestinal disease, is the best predictor of disease severity. The lack of association between CRP and physical symptoms is difficult to understand but may relate to many asymptomatic patients.

The second component of these results is the relationship between HADS and physical symptom scores HBI and CAI. Here we find that both HADS anxiety and HADS depression scales correlate strongly ($p<0.00001$) with HBI in Crohn's Disease and CAI in Ulcerative Colitis. This is further supported by the fact that a past history of depression or anxiety illness and experience of psychiatric treatment leads to an increase in present reporting of physical symptoms for both Ulcerative Colitis and Crohn's Disease. Why should physical symptom scores correspond strongly with psychiatric symptoms but only variably with disease severity?

There are several possible explanations for these findings.

i) HADS and physical symptom scores may be measuring similar things

In a literal sense, HADS scales include questions about low energy and malaise as do CAI and HBI. Alternatively, it may well be that patients who are likely to report lots of symptoms on one checklist are likely to do so on another. Correlation is simply a function of responder style.

ii) There exists a common biology implicated in both gastroenterological and psychiatric symptoms. Nervous innervation of the gut from the parasympathetic and sympathetic nervous system is likely to be affected by anxiety through noradrenergic and adrenergic pathways. The presence of bowel frequency and urgency are likely to be related to sympathetic nervous system and anxiety. This connection may exist irrespective of the level of inflammation. Vagus innervation of the gut is partly moderated by Serotonin which is implicated in depression. (Although serotonin does not cross the blood brain barrier, such an explanation cannot easily be given.) Thus, it would be possible to separate the physical symptoms of pain, urgency, nocturnal defaecation and frequency from a quantitative level of inflammation.

iii) Physical symptom reporting is accentuated in depression. Patients may notice physical symptoms more. Pain scores are higher in depressed subjects.

iv) The most distressing aspect of having IBD is presence of symptoms. Waking to pass stool, frequency and urgency could be the most distressing aspects of having this illness. Quantitative levels of inflammation may be less important in terms of quality of life than disability caused by symptoms.

The third component of these associations is that there appears to be no correlation between psychiatric symptoms and any inflammatory markers. HADS Anxiety and Depression scales do not correspond with CRP, ESR, WCC and Faecal Calprotectin in both

Ulcerative Colitis and Crohn's Disease. (Of incidental interest is the finding that low Hb in both illnesses corresponds with higher depression scores which is consistent with anaemia being a well understood cause of depressive syndrome. This is reassuring as it suggests that serology can in fact be associated with psychiatric symptoms consistently with previous literature).

This finding is perplexing in the context of the thesis.

i) Depression is associated with changes in IL 2, IL6 and IL 10 and TNF alpha. These cytokines are on the pathway for CRP levels. Depression should associate with CRP and consequently ESR.

ii) Faecal Calprotectin is a strong marker of intestinal disease. Depression (or anxiety) should be likely to correlate to severity of disease even indirectly via symptoms.

The possible explanations for this are

i) The relationship between depression and inflammatory changes has been based on patient populations without acute inflammation. Patients with known autoimmune illness are generally excluded from studies of depression and inflammation.

ii) The literature on psychoimmunology does not include severe levels of inflammation. It could be possible that above a ceiling level of inflammation the relationship does not exist

iii) CRP and ESR are poor markers. In much of the literature, HS CRP is used rather than normal CRP. It is possible that if cytokines were measured these would be altered.

iv) The contribution of inflammation to depressive symptoms is small. This contribution is superseded by distress incurred by physical symptoms.

In summary the relationship between affective symptoms, physical symptoms and inflammation is complicated. Results from this study go against the literature on psychoimmunology but are consistent with findings from clinical studies about a strong relationship between physical and psychiatric symptoms.

7.1.8 The role of corticosteroids in affective disorder in the IBD population

A primary hypothesis of this study is that corticosteroids are an independent predictor of affective illness in this population. The results showed that in patients with Ulcerative Colitis or Crohn's disease by univariate analysis 85 patients who are presently on Prednisolone compared with 578 who are not have significantly higher HADS Depression scores (p=0.026) but no difference in HADS Anxiety Scores (p=0.959). This supports the hypothesis that being on Corticosteroid medication predicts higher levels of depression symptoms but not anxiety symptoms. Secondly, having been on Prednisolone in the past year (but no longer being on the medication) is significantly associated with higher HADS Depression (p=0.033) but not

HADS Anxiety (p=0.081). Thirdly increased duration of prescription is related to higher depression scores, but dose is not. A fourth finding is that neither being on prednisolone nor having been on prednisolone is not significantly related to an increase in ASRM mania symptoms (p=0.172, p=0.501). Similarly, neither dose nor duration has any effect on the presence of manic symptoms.

The finding that usage of corticosteroid medication is a predictor of depression is consistent with a large body of literature suggesting that this should be the case. As described in chapter 2, high levels of corticosteroid affect amygdala and hippocampus and are analogous to a chronic stress state. The finding that those who have been on corticosteroids but are no longer, is also consistent with a chronic stress model of depression. Furthermore, those who have ceased corticosteroids often report dependency symptoms. The finding that duration of prescription is associated with depression is also consistent with neuro endocrinological literature. The main difference from other studies is that dose of steroid does not appear to play a role. Early work into the psychiatric side effects of steroids pointed to the observation that patients would experience noticeable mood swings in the first days to weeks of starting a medication but that this effect would lessen over time. In looking at subjects in this study who have been on corticosteroid for a week we do not find this. This may be due to the fact that the experience of physical illness or other factors play a larger role in depressive symptomatology. Furthermore, in earlier work the presence, nature or severity of the physical illness is not measured. Thus, the depressive symptoms observed at the time of steroid prescription are attributed to the steroids alone. As this part of the discussion is

focussing on univariate analysis, we will not concentrate here on the effect of disease symptoms or severity of inflammation as confounding factors yet.
It would be important to conclude however that patients with IBD who are on or who have been on steroids for a long time are more likely to experience depressive symptoms. These patients would be a target group for screening.

HADS anxiety does not correlate with corticosteroid usage. It would be imagined that this should do. The omission from the literature about anxiety may relate more to a publication bias rather than an absence of anxiety not relating to the HPA axis. Is there a separate biology underpinning anxiety and depressive illness which can be highlighted through the HPA axis dysfunction?

An important finding is the lack of relationship between corticosteroid usage and ASRM manic symptomatology. Previous literature would suggest that a high dose of corticosteroids would cause an acute manic/psychotic reaction. The likelihood of this reaction would be determined by dose of the steroid and that potentially everyone could have such a reaction given a high enough dose. The findings from this study contradict this. Unlike other studies, ISA measures manic symptoms as a continuous measure rather than categorical diagnosis. As such it is possible to detect that some patients may notice some affective symptoms suggestive of mania (such as poor sleep, higher energy etc) but who do not have a full syndrome. It is clear that while many patients acknowledge some of these symptoms, they do not appear to correlate to corticosteroid medication. Furthermore, there is no effect of corticosteroids on the onset of manic symptoms. The literature reports that corticosteroid induced mania/psychosis occurs between 3-7 days of starting the

medication. We can show that that there is no increase in these symptoms in this time frame. The conclusion here is that a manic/psychotic episode caused by corticosteroid medication is likely to be an idiosyncratic response in predisposed patient rather than a dose effect. This is important as it suggests that, by analogy, environmental stress may only precipitate psychosis or mania in some individuals rather than it being a risk factor for all given a sufficiently major stressor.

The limitations of these findings may derive from the measures used in the study. The ASRM has not been used in a medically ill population. Typically, it is used more for measuring change in a patient with diagnosed mania. The lack of categorical diagnosis could also be questioned but the main premise has been that manic side effects are dose dependent on corticosteroid and thus a dimensional measure appears more appropriate. Of note psychotic symptoms were not measured and thus no conclusion can be reached about a purer schizophreniform (and not polymorphous affective) psychosis and its relationship to corticosteroid usage.

7.1.9 Role of anti TNF immune modulators in depression

A number of studies have pointed to a higher level of TNF alpha in patients with depression. Other studies, from work on patients with autoimmune illness, have shown an increase in mood prior to any change in physical health indicators, when these patients have been prescribed anti TNF medication. (239)

There have been three main hypotheses for the involvement of pro-inflammatory cytokines in the activation of depression. As discussed in chapter 4, IL-6 and TNF-alpha are thought to either decrease levels of serotonin in the brain or activate the HPA axis (239, 240). One study describes an activation of the neuronal serotonin uptake transporters by these cytokines. (241) Other studies found that pro-inflammatory cytokines activate serotonin degrading enzymes (242). Both of these theories suggest that certain pro-inflammatory cytokines cause a decrease in synaptic serotonin which contributes to the developing depression. Another theory suggests that these cytokines have a role in depression related activation of the HPA system (243, 244).

There have be many articles published which report a decrease in depressive symptoms in patients receiving Infliximab (IFX). As described in Chapter 4, it has been suggested that infliximab as well as other TNF-alpha antagonists may be therapeutic for somatic, cognitive and affective symptoms associated with the depressive symptoms in BD. It has remained unclear whether infliximab is having a direct therapeutic effect on depressive symptoms or whether it acts indirectly through relieving the autoimmune symptoms.

One study looked at 6 Crohn's disease patients on infliximab and showed that on Day 7 and 56, when plasma levels of IFX decrease following last injection there was an increase in HADS, CDAI and CRP scores overtime. (229) There was a correlation between physical symptoms and HADS. A further study looked at 23 CD and UC patients and showed that IFX

treatment was associated with a decrease in depressive score on IBDQ, and an increase in QoL. (247)

In a study of 92 CD patients and IFX treatment was associated with more anxiety at time of injection but fewer depressive symptoms compared to other treatments. (248) One study followed 14 CD patients and IFX treatment showed a significant effect in reducing depression scores on CES-D. (249) Persoons et al. 2005 studied 100 CD patients and IFX treatment decreased the risk of earlier retreatment, improved CDAI and CRP scores. (250) Importantly there was a correlation in depression score and well-being in total group. However, it can be noted that it is impossible to determine in most of these studies whether the reduction in depressive symptoms relates to the IFX directly or whether this is a consequence of increased quality of life, decreased inflammation or decreased symptoms. Interestingly those with a high baseline serum CRP show a significant improvement in depression compared to control, whereas patients with normal CRP show no difference.

The ISA study lacks longitudinal dimension which would allow a clearer understanding of the relationship between anti TNF medication and depression. However, it is powered to be able to control for the effects of inflammation and symptoms on the relationship between medication and affective disorder. The results from ISA show that patients on infliximab have lower levels of depressive symptoms (HADS-D) than those who are not on infliximab. These patients have no significant differences between their levels of symptoms, CPR, ESR, WCC and faecal Calprotectin. If anything, it is likely that those receiving infliximab are more likely to have (of have had) severe disease. Therefore, infliximab is probably associated with lower depressive symptoms and this reduction is not likely to be due to lower inflammation

or physical symptoms. The same is not true for Adulimamab but this may be due to powering effects. Just 12 patients were on Adulimamab at the time of study. There are two potential questions related to this finding. Firstly, it is possible that the reverse direction of causality is possible. Patients who report more symptoms due to their depression may be offered Infliximab. Lastly there may be a non-pharmacological benefit of Infliximab. Infliximab is offered by infusions and is generally delivered by specialist nursing staff. It is possible that the nurturing or even placebo effect of this delivery mechanism may itself be anti depressive.

7.1.10 Socio Demographic predictors of GI symptoms

There exists a widespread literature on the social determinants of health. General consensus exists that poverty and social inequality lead to increased levels of disease across the world. The ISA study includes data pertaining to social class, unemployment and other variables that facilitate the opportunity to look at this in an IBD population.

Importantly, unlike many larger studies, data exists which includes physical symptoms, disease activity and sociodemographic variables.

Gender is a common factor which has been looked at in terms of relationship to physical health measures. In the ISA cohort, consistent with other literature it can be seen that female gender is associated with higher levels of physical symptoms although there is no

relationship between gender and inflammation markers. This, as discussed above may be due to higher levels of depressive symptoms but also may represent sociological factors relating to socially derived gender differences and differences in health seeking behaviour. (237)

When social class is addressed, we can see a significant trend towards higher physical symptom reporting in lower social classes. A trend towards a lower social class is represented by a higher level of symptoms. Concurrently there is no change in any inflammatory marker between social classes. This means that disease activity is non-significantly differentiated by social class, but symptom reporting is. It is perhaps unusual that quantitative levels of disease are not, in fact, higher in lower social class.

There are a number of ways this could be explained. Firstly, lower social class could be causative of higher levels of physical symptom reporting. This could be due to the experience of more social adversity of which disease was one of many difficulties causing more distress. Those in lower social classes may be experiencing higher levels of depression and anxiety and thus physical symptoms (as can be seen above) reflect this. Higher symptom reporting may also reflect style of engagement with health services. Are patients likely to be taken more seriously if they mention more symptoms?

Secondly more physical symptoms may be causative of occupational situation and consequently social class by the terms used in this study. Those who had previous severe disease (but not now) may have lost jobs or not attempted nor succeeded in job promotion. Those who experience more symptoms may struggle to perform at work or may be less

likely to seek promotion. Those who experience more symptoms may be less likely to have completed education.

There exists a literature which considers the role of social class and post code in relation to IBD. To date there is no evidence that IBD is differentially represented by social class. Furthermore, geographical living situation does not reflect this. Much public health literature is dedicated towards social determinants of health. However, this work often does not have both subjective symptoms and objective inflammatory markers.

A third possibility would include confounders relating to both symptom reporting and social class. Here personality features and psychiatric illness may play a role. Patients with higher levels of external locus of control may be more likely to report symptoms and may be less able to attain higher skilled jobs. Patients with aspects of certain personality disorders may be more help seeking and equally may struggle to progress in workplace environments.

Following on from this, perceived stress (not measured) may be higher in lower social classes. This may be expressed in this study in terms of physical symptoms.

In terms of multiple adversities leading to higher symptom reporting, it can be noted that neither marital status nor household composition predict change in symptom reporting for either Crohn's disease nor Ulcerative Colitis. Age, smoking nor alcohol consumption status is predictive of symptom reporting variation. Importantly employment status and consequent incapacity benefit status do predict symptoms but not disease activity. This suggests that of factors associated with social adversity and deprivation, it is work above all others which

relate to reporting symptom irrespective of level of disease. Consistent with this, is the fact that those who have been previously on incapacity benefit (but no longer are), have higher symptom scores than those who are but lower scores than those who have never been on ICB. This would suggest that it could relate to level of meaningful activity which predicts symptom reports irrespective of disease activity.

Another finding consistent with this is that those who are self-employed have lower levels of symptoms compared to those who are employed. Self-employment by definition requires strong internal locus of control. In the absence of sick pay, those who are self-employed should have higher need to dismiss symptoms.

One further finding in this group is that those who drink alcohol have higher levels of symptom reporting in spite of no differences in disease activity. There is an arguable "J" shaped curve relating to physical symptoms and units of alcohol consumption. Here those who drink large amounts and those who do not drink at all have higher levels of symptoms. This may relate to background levels of mental illness – those who are able to drink moderately may be the most mentally healthy.

An initial hypothesis could be that symptoms relate to a social function. The experience of a symptom and the need to voice this could relate in some way to there being someone to voice this to. However, this section of the results shows that neither marital situation nor household composition differ with regards to symptom reporting.

We will see in the discussion of multivariate analysis the role depression may play in mediating some of these associations. However, from what can be seen here, meaningful activity as measured by social class and employment status appears to be a predictor of physical symptoms in the absence of variance in inflammation.

7.1.11 Multivariate analysis

Thus far the results discussed have related to univariate analysis. Both psychiatric and physical symptom measures have been associated with social, clinical and pharmacological predictors. There is a clear association between gender, employment, incapacity benefit status, marital status, physical symptoms, corticosteroid medication, infliximab, surgery and disease phenotype and depression and anxiety. There is also a clear association between socio demographic factors and physical symptoms.

The multivariate analysis was conducted using forward stepwise regression. In patients with Crohn's disease employment status, incapacity benefit status, and Harvey Bradshaw index were independent variables predicting both HADS anxiety and HADS depression.

There are several important interpretations of this finding for Crohn's disease. Firstly, this shows that physical symptoms are independently correlated with depression and anxiety. This correlation is independent of disease severity (as measured by inflammation), historical disease severity (as measured by surgical history, presence of stoma, duration of disease or age of onset) or prescribed medication as a proxy for disease relapse. This can be taken to

mean that those reporting high levels of physical symptoms have a stronger likelihood of depression than those with “worse” disease. This could mean that whatever the medical history of a patient with Crohn’s disease, it is reporting of physical symptoms which is most likely to indicate a raised likelihood of a depressive or anxiety illness.

Secondly the presence of both employment status and incapacity benefit status as independent variables from each other is interesting. The fact that employment, or lack thereof, relates to the presence of depression and anxiety is not surprising. However, the fact that both employment status and in addition the present or past receipt of incapacity benefit is curious. This may represent two different mechanisms leading to depression. This follows a previous study wherein both unemployment and social deprivation are independent risk factors for affective disorder in IBD. (238)

Before discussing this point further, it is important to note that while gender, marital status, smoking and alcohol are predictive of mental state in univariate analysis, these effects are not independent of employment and benefits. Thus, the social determinants of mental health appear, in this population, to derive from meaningful activity. This appears to be more important than severity of disease (as measured by the factors listed above). Thus, it is not the fact that a patient may have undergone several surgical procedures, nor that they have active disease but how they are able to subsequently return to work or role which predicts whether they will become depressed.

The independence of employment status and incapacity benefit status is interesting. This would suggest that having a job is important but that when unemployed the decision to

receive incapacity benefit is also important. The decision to receive benefits may represent a series of psychological processes. From the data in this study, it would seem that such a decision and its ramifications for subsequent depressive illness, does not depend on severity of illness. If a patient with Crohn's disease receives incapacity benefits, their likelihood of depression does not derive from severity of illness even if it is that severity of illness which may have led them to receiving these benefits. Thus, it may be perceived loss of long-term role which may be the most important element predicting depression or anxiety.

The findings in Ulcerative Colitis differ from those in Crohn's disease. Independent predictors of anxiety are incapacity benefit status, prednisolone in the last year and the colitis activity index. Independent predictors of depression Ulcerative Colitis are incapacity benefit status, prednisolone in the last year and gender.

The presence of incapacity benefit status in both illnesses supports the hypothesis that the lack of meaningful activity irrespective of disease severity is a pathway into depression and anxiety. Here the absence of employment status is curious. As there is less unemployment in the UC group it may be that those who are unemployed are not so because of their illness. Whereas those on incapacity benefit are likely to be either the worse affected by illness or those who have other reasons for needing these benefits.

Unlike with Crohn's disease, gender is an independent risk factor for depression in UC. This is an unusual finding as other literature has shown that there are many characteristics of Crohn's including infertility, obstetric complications and body dysmorphia secondary to higher rates of stomas which might suggest that women are more likely to be depressed.

Univariate analysis clearly shows that female gender remains a predictor of depression in Crohn's, but this appears to be accounted for by other more depressogenic factors. The finding that female gender is a risk factor for depression at all is completely consistent with a large body of evidence.

Finally, the finding that being on Prednisolone in the last year is an independent risk factor for depression in UC is an important finding from this study. While there exists good rational for the finding that corticosteroids should cause depression, this is the first study to find that this is the case when controlling for severity of illness, in terms of present symptomatology and inflammation. This finding has important implications for the management of all auto immune illnesses including asthma, eczema, rheumatoid arthritis and COPD. Should corticosteroid medication in and of itself lead to depression, its long-term prescription should be considered carefully in the management of chronic illness. This should give rise to the need to screen those on long term corticosteroids for depressive illness.

7.2 Methodology and Limitations

7.2.1 Strengths of study

The study was able to gain a large sample size; larger than any similar study of IBD. This made predictors of depression and anxiety possible for which many other social and clinical variables could be controlled. There were some aspects of data for which the number of samples was low such as faecal Calprotectin and prescription of inflixamab for which only up to 50 samples existed. However, overall statistically significant results were found when corrected for multiple comparison tests.

It can be argued that there was little in the way of selection bias from the sample. Some 76% of clinic attenders responded to the study. When looking at those in the original cohort compared to those captured up to 10 years later, there were no significant differences in terms of clinical or demographic data. This would suggest that those entering the study were a fair representation of an out-patient clinic population.

The study gained from having both a prospective and cross-sectional arm. This has not been done in other studies of psychiatric phenotype in IBD. Unlike other IBD studies all subjects had a histological diagnosis of IBD. This study is unique in having biological, psychological and sociodemographic data from this patient population.

Three areas which have been ignored in this study are personality measurements, perceived stress scales and life events recording. There is an existing literature on both of these and

while they may have added more to explain the variance of depression or anxiety in this group, they were omitted due the practicalities of extending the demand on subjects to participate.

Below is a critique of the methodology of the study in component parts.

7.2.2 Limitations

7.2.2.1 Sample

As outlined in the methodology section of the thesis, patients recruited to the ISA study were those with a histological diagnosis of IBD, aged 18-65, fluent English speakers and were attending a routine outpatient appointment at the gastroenterology department of the Western General Hospital, Edinburgh.

The likely omissions in this group were those who had quiescent IBD and required no routine appointments during the sampling timeframe or those with severe illness such that they were inpatients in the above or another hospital. There exists a small private health sector in Edinburgh which may have seen some IBD patients, but the number is unknown though likely to have been small. The importance of this relates to whether a representative sample of patients according to social class, smoking, employment and alcohol usage was recruited in the study. Those who were very well or very unwell may have skewed the sample in both directions. However, given that 77% of the potential sample were recruited,

it may be fair to assume that this was representative. Following previous work, it may be deduced that those in remission/relapse would be likely to demonstrate altered levels of psychopathology though this could push the results in both directions, but the magnitude of this effect is unknown. In terms of general demographics, only four patients were approached who were unable to participate in the study due to problems with language; two of these did not have English as a first language, one was illiterate, and one had a learning disability. These patients are unlikely to have affected any results significantly and were ignored from the results and discussion.

The prevalence of IBD varies internationally and Scotland may have higher levels than other countries. (204) The rates of depression in Scotland may also be higher than other countries, thus this sample could either represent potentially higher levels of psychiatric illness than that which may be seen elsewhere.

In comparison with other work, the ISA has one of the largest sample sizes for this population. As has been described in the introduction, work in this field has either centred on a community sample which may not have histological diagnoses of IBD or hospital samples which are much smaller. It can be concluded that the ISA sample is likely to be representative of an out-patient population in a developed country and the psychiatric phenotype and socio demographic characteristics are likely to be representative of an IBD population.

7.2.2.2 Coeliac disease

Coeliac disease was chosen to be a comparator group for several reasons outlined in the introduction. Patients with coeliac experience chronic gastroenterological illness with similar symptoms to IBD, need for hospital out-patient appointments, contact with the same gastroenterologists as those who would see the IBD population. However, Coeliac disease patients would not exhibit clear inflammatory disturbance, although inflammation can be detected in the small intestine, use anti-inflammatory medication, use corticosteroids (except in extreme cases), surgery, in-patient admissions. Coeliac disease is unlikely to have impacted on patients' lives including being able to maintain a job or a relationship in the way that IBD may do.

Thus, the use of coeliac may have allowed a comparison of the experience of illness but without inflammation, steroid use and disability secondary to illness and intervention. Coeliac disease was also used to be able to control for the rates of depression by socio demographic variable. As can be noted from the results the number of coeliac patients is significantly smaller than the IBD group, however this has not affected the ability to power the main comparisons needed for the above questions. A question does arise as to the representativeness of the coeliac group recruited. As described in the introduction, patients with coeliac, when they get a diagnosis, need simply to adhere to a dietary plan. There is little in the way of medical intervention which is required. Coeliac can therefore be managed in a primary care setting. However, patients in this study all attended a secondary care coeliac disease clinic. This may suggest that they had complicated disease or exhibited comorbidity which was not able to be managed in primary care. As will be discussed below,

this group showed similar levels of psychiatric illness as the IBD group which may reflect how they were atypical coeliac patients.

7.2.2.3 Prospective data

Data for the ISA study comes from both the prospective and cross-sectional components. The prospective work was carried out between 2001 and 2005 and recruited sequential referrals to the IBD clinics for clinical phenotyping and genotyping. Patients were recruited based on diagnosis and willingness to participate. It is not known how many patients refused to participate in these rounds of data collection. However, for the purposes of gastroenterology research, participation in research is unlikely to be subject to sample bias in the same way as in psychiatric research. Personality and social class are unlikely to affect understanding pathogenesis of IBD in this work. Over many years the IBD group recruited 2000 patients. However only some of these consented to specific aspects of the research and therefore there will exist some sampling bias where psychiatric phenotype is looked at latterly.

Initially the study design aimed to recruit all those who were registered with the IBD database, however this excluded many new patients and furthermore many of the original patients were not attending outpatient appointments in the timeframe of the cross-sectional arm of the ISA study.

As can be seen, of 1160 patients with data, some 490 had deceased, moved area or were not due to attend clinic in the cross-sectional arm timeframe. However, when we compare

those in the cross sectional who were in the original cohort with those who were not, there are no significant differences in these groups with respect to age, age at diagnosis, family history, Vienna classification at diagnosis, number of surgical procedures and smoking status. These comparators, while not exhaustive, reflect a general appraisal that disease type, disease severity and socio demographic variables were not significantly different. This suggests that those patients who were initially recruited were not significantly different from those who were seen in the cross-sectional component of the study.

There remains an important question as to why over 10 years some 490 patients were not captured in the cross-sectional component of the study. The possible clinical course of IBD allows for remission, remission following surgery or time between relapses lasting several years. Although not measured in this study, the ethnicity of the ISA cohort was anecdotally largely white Scottish and did not present with the same level of migratory population as may have been seen in other illnesses or locations. The mortality rate in IBD is not very high such that it is unlikely that a large proportion of patients will have died over the 10-year period. The implications for psychiatric phenotyping are that, a proportion of patients entered into the study may have had mild disease and did not need to attend clinic which may have been associated with lower levels of psychopathology. Thus, the rate of psychiatric symptoms in IBD may be slightly higher in ISA sample. Alternatively, those who did not attend clinic during this time may have done so because of extreme social adversity. Importantly those who were/were not recruited to the initial cohort showed no differences in levels of psychopathology.

7.2.2.4 Measurement used in the ISA study

The following section will look at the measures used in the ISA study to identify any methodological flaws which may be as a consequence of choice of measures used. This will be divided into sociodemographic data, medication data, IBD disease data and psychiatric measures.

In terms of sociodemographic data, much of the acquired data has relied on self-reporting measures. Here it is likely that subjects will under report smoking and alcohol usage. It is also possible that subjects may under estimate reliance on incapacity benefits and level of employment. Social class estimates have been based on self-report of occupation and extrapolation to I-VI social class definitions. Many patients in the study were students and were excluded from this definition. There are many ways in which social class can be defined and there exist more recent and accurate definitions. The system used here, while imperfect, simply represents a traditional and well used model.

The use of self-reporting of medication prescription is open to some discussion. Patients may frequently forget or be unaware of the name, type and dose of their medication. Here both generic and brand name was used to try and cover most treatments. It is true that a better account of medication would have been a cross reference with GP records and pharmacy records. However, this was out with the scope of the study and not completed. Patients with a chronic severe illness such as Crohn's or Colitis are often very likely to have great awareness of their medication. Of most importance was the prescription of steroids.

Evidence suggests that patients are very aware of being on steroids due to side effects and can often describe dose accurately.

As discussed in the methodology section, much attention was paid to the use of the HADS scale as the primary measure of psychiatric phenotype. There were clear disadvantages in its use as this was a self-reported scale and could primarily give dimensional rather than categorical descriptions of psychopathology. Given that the HADS has been used extensively over the PHQ, Zung and Beck in IBD populations, it was deemed the best one to use so that results could be easily compared with other studies. In this study the HADS scale has been used as a dimensional scale with separate anxiety and depression arms rather than with cut offs. The main reason for this is that the cut offs are often arbitrary, and it was important to try and pick out patients with subclinical levels of depression and anxiety symptoms. Some of the main hypotheses were that steroid levels and inflammation levels were associated with mood. In this case it would be important to measure all variables as continuous rather than categorical data as in theory, small increments could cause subtle changes in mood. A further question relates to the division between anxiety and depression subscales. Much of the interest in co morbid mental and physical health relates to depression, and on this basis, it was important to get a pure depression scale. Furthermore, the available evidence suggests that depression, but not anxiety is likely to relate to corticosteroid usage. As the study was sufficiently powered to study this, most of the analysis was conducted with separate depression and anxiety outcomes.

There exists an extensive literature on screening for depressive illness. There are already a number of tools available for this purpose and there have been several reviews assessing the range of tools available (207)

Pooled data on specific instruments is available for the Centre of Epidemiology Studies-Depression scale (CES-D), General Health Questionnaire (GHQ), Medical Outcomes Study Depression Screen, and the Symptom Driven Diagnostic System-Primary Care scales. More recent literature exists on bivariate meta-analysis of Patient Health Questionnaire-9 item (PHQ-9) and 2 item (PHQ-2) instruments. (208) However, these scales were not compared with the other depression identification tools in clinical practice.

The Cochrane Collaboration (208) published a meta-analysis of depression screening tools with bivariate outcomes. Importantly most of these analyses were not carried out in medically ill populations.

Evidence was taken from the NICE guideline review group looking at the optimum scale for measurement in a medically ill population. This review was limited to identification tools used in UK clinical practice, that is, the BDI, PHQ, GHQ, CES-D, Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), Zung Self-Rating Depression Scale, and any 1- or 2-item measures of depression in primary care, hospital and community settings. 'Gold standard' diagnoses were defined here as DSM-IV or ICD-10 diagnosis of depression. Studies were excluded if they did not clearly state that the comparator was DSM-IV or ICD-10, used a scale with more than 28 items. (208)

Of 129 studies, 77 studies were conducted in primary care or general medical settings and 52 were on people with a chronic physical health problem. 16 were on the PHQ-9, five on the PHQ-2, seven on the Whooley, 18 on the BDI, five on the BDI short form, five on the BDI

fast screen, 28 on the GHQ-12, 17 on the CES-D, 27 on the GDS, 26 on the GDS-15, 24 on the HADS-D.

Of the above scales only the HADS and the ZUNG have validated measurements of mild, moderate and severe depression.

The Patient Health Questionnaire (PHQ) (211) in both consultation and chronic physical health problem populations was found to have good sensitivity and specificity.

The Beck Depression Inventory (BDI) (210) and subsequently the cognitive–affective subscale of the BDI has often been used to identify depression (210). The BDI appeared to perform relatively well in terms of sensitivity (0.85, 95% CI, 0.79, 0.90) and specificity (0.83, 95% CI, 0.70, 0.91). However comparable sensitivity (0.85, 95% CI, 0.79, 0.89) but lower specificity (0.73, 95% CI, 0.65, 0.79) was found for this scale in people with a chronic physical health problem.

Data from the BDI-fast screen (210) were combined to assess the impact of removing somatic items since data from both scales were relatively sparse. There was sufficient, although relatively low, consistency between studies to assess these scales (BDI: non-somatic) in consultation populations and those with a chronic physical health problem. In populations with a chronic physical health problem, the BDI non-somatic scales performed relatively similarly. The instruments were associated with relatively high sensitivity (0.87, 95% CI, 0.62, 0.97) and but reduced specificity (0.74, 95% CI, 0.65, 0.82).

The General Health Questionnaire (GHQ) (211) was developed as a general measure of psychiatric distress and measures a variety of constructs such as depression and anxiety. There were only two trials of the GHQ-28 in patients with a physical health problem. There was relatively high sensitivity (0.84, 95% CI, 0.59, 0.95) but less specificity (0.75, 95% CI, 0.70, 0.79) found for this scale in people with a chronic physical health problem.

The Hospital Anxiety and Depression Scale (HADS) (213) is a measure of depression and anxiety developed for people with physical health problems. The depression subscale has seven items and the cut-off is 8 to 10 points. A total of 21 studies have been conducted, however meta-analysis could not be conducted due to very high heterogeneity for all subgroups including consultation populations and older adults. Notably this scale has been used extensively for patients with Crohn's disease and Ulcerative Colitis. (See chapter 3)

In view of the many possible available scales, the decision was made to use the HADS as:

1. Sensitivity and specificity compared favourably with all other scales
2. Both sensitivity and specificity became lower in other scales when used on a medically ill population
3. The HADS has been extensively used in populations with Crohn's Disease and Ulcerative Colitis
4. The HADS has been used on other English-speaking Scottish populations of similar demographic

Little literature exists as to measurement of manic symptomatology in a medically ill population. As discussed in the methodology, most scales looking at mania are either a

categorical diagnosis or severity based in patients with known illness. It is likely that ASRM was insufficient to detect new cases of bipolar illness – if anything scores correlated well with HADS scores which may mean, at best, they are another measure of affective illness.

The use of self-reported measures of past psychiatric history may also be questioned. An improved way of doing this would have been to cross check self-reports with GP data and psychiatric records. This was beyond the scope of the ISA study but based on result which patients provided, past psychiatric history appeared to be reported in a range expected by epidemiological data.

The gastroenterological scores used (CAI, HBI) are well validated tools used in many similar studies. Of note, some of the symptoms in these scales could apply to both physical and psychiatric symptom scores such as general malaise. Before the actual study the IBDQ was trialled in a pilot but it was clear that to gain an optimal sized sample a shorter questionnaire would be best. The advantage of the prospective element of this study is that all data relating to disease staging and typing and all surgical history was collected blind to future psychiatric assessments. Here both Vienna and Montreal classification systems are well validated systems of classifying IBD.

Many of the original hypotheses for this study had been predicated on the idea that specific inflammatory changes notable IL-2, IL-6, IL-10 and TNF alpha were abnormal in both depression and IBD. As can be noted these were not measured in the patient group due to

the study design. Measurements of inflammation used were CRP, ESR, WCC and faecal calprotectin. The correlation between these markers and the above cytokines may not be ideal but may have represented a rough measure of inflammatory process. Of note Hs CRP has been the measure used in many of the depression studies in this area. The choice of these markers was based mainly on their easy availability in a clinic setting and the fact they would have been routinely done on the patients. Work on cytokines in depression has mostly been conducted in psychiatric populations who are medically well. Thus, this represents an early piece of work in looking at patients with known inflammation and psychiatric phenotype. Of note not all patients underwent inflammatory markers collection. Those who did would be patients needing closer monitoring of their illness which may reflect a deterioration or improvement in their condition. Patients with long term stable illness would not have been investigated. This does not diminish the relationship between psychiatric phenotype and inflammation however as patients were not selected because of known levels of psychiatric phenotype or known inflammatory levels. Those who gave samples for faecal Calprotectin levels were likely to have more severe disease and are therefore a smaller group.

7.3 Discussion: Implications of the main findings and future research

7.3.1 Prevalence of psychiatric illness in IBD

A first and consistent finding from this study is that depression and anxiety remain high in the target population. While this finding is not new it supports other literature that this is the case and it remains worrying that a large number of patients with IBD not only have high levels of depression and anxiety, but a significant proportion are undiagnosed and untreated. These findings support the development of liaison psychiatry services in gastroenterological illness. Awareness that comorbid depression does lead to increased health service usage highlights the strong argument for integrated care in this area.

7.3.2 Disease predictors of Depression

In the univariate analysis, we see that patients who have strong surgical histories, have a stoma and who have oral disease are more likely to have a depressive illness. Such findings support the idea of targeted screening in such patients.

7.3.3 Socio demographic predictors of depression

The strongest predictors of psychiatric phenotype in this population were unemployment and incapacity benefit status. There are two implications from such findings. Firstly, as above it can be argued that the group of those on ICB or unemployed could be high risk groups who should be screened for depression. The second implication is that, beyond

severity of illness, it is loss of role or lack of meaningful activity which is closely associated with mental health. These themes are often taken up in Interpersonal therapy and to a lesser degree in Cognitive Behavioural Therapy. This tells us that specific therapeutic targets such as cognitions around usefulness and purpose may be the key to understanding depression in this population. It also implies that there may be a role for supporting patients back to employment may be useful in managing long term medical conditions in ensuring patients are able to work or be active in some way.

7.3.4 Physical symptoms and psychiatric symptoms

The finding that there is a close and independent relationship between physical symptoms and psychiatric symptoms is not new. However, given the available data in this study of inflammatory markers it adds new implications to the literature. Having an objective measure of disease severity in this study shows that mood is a far stronger driver than inflammation in expression of physical symptoms. While the patient's history should never be ignored, an interesting question is to what degree physician's decision to investigate a patient or treat a patient is based on history rather than objective findings. That is not to say that symptom management is not a reason for not treating or operating but to highlight the possible role of psychology or psychiatric illness where there is a significant disparity between reported symptoms and quantitative disease. Highlighting such a finding to gastroenterologists may reduce the need for unnecessary investigations and surgery. The literature around medically unexplained symptoms become complicated when patients have an actual physical disease and their symptoms can, in part, potentially be explained by that disease. In IBD this study can show that mood and anxiety drive symptoms considerably

more than disease which would be useful information for a gastroenterologist to take in to clinic.

7.3.5 Corticosteroids as predictors of depression

Arguably the most important finding from this work is that corticosteroids represent an independent risk factor for depression – independent from severity of disease or physical symptoms. It is not surprising that this is the case given what has already been discussed but this is the first study to show this. Patients on long term steroids should be screened for depression. It can be stated that their depression is not just a product of chronic disease but the steroids themselves. This has clear implications for almost every medical specialty and the chronic disease management of asthma, eczema, COPD, arthritis etc. The importance of this finding is also that it can argue for a change in the role of Liaison psychiatry. Hitherto it has been the role of liaison psychiatrists to advise medical teams on the psychiatric management of their patients. This finding would support the idea that the decision to initiate/continue/discontinue different immunotherapies (including corticosteroids) for a physical illness could be as much a psychiatric as a medical decision.

7.3.6 Corticosteroid dose does not predict mania

The available literature suggests that dose increase of corticosteroids leads to a manic/psychotic reaction. This study refutes this idea as there appears to be no relationship between steroid dose and affective symptoms across a large population. This study suggests that a manic or psychotic reaction to steroids is an idiosyncratic reaction and that those who

experience this must have some genetic predisposition to this. This may be comparable to puerperal psychosis or drug induced psychosis.

7.3.7 Anti TNF medications increases mood

Consistent with other literature, this study shows that anti TNF medications increase mood. While a prospective study would be able to demonstrate causality better, here we are able to show cross-sectionally that the increase in mood does not correspond to differential inflammation levels, symptom scores or severity of past illness. This finding may not have direct applicability to a gastroenterological environment as it would be hard to argue that in this group, such agents should be used principally for its antidepressant action however it supports its usage in depression and much can be learnt from the experience of this drug in gastroenterology.

7.3.9 Future research

There exist several lines of future research which hopefully can emanate from this study.

7.3.9.1 Untreated depression in the outpatient population

It would be interesting to further research the factors which lead to poor detection and treatment of depression in this patient group. While obvious answers would include the lack

of resources and skills to do so, other ideas such as stigma about mental health or how to improve access to psychiatric case notes may aid this.

7.3.9.2 Cognitive schema of those with depression in the medically ill

What are the underlying common features of those who have IBD and are depressed? Do those with either depression or anxiety have negative thoughts about appearance, social anxiety with regards to bowel frequency or urgency or generalised feelings of failure?

7.3.9.3 Immunological basis of depression in medical illness

The ISA study was unable to look at specific immune markers such as TNF alpha, IL 2,6,10 which have shown to be elevated in depression. The study has shown that inflammatory markers measured do not vary significantly with mood. However, it may be that more sensitive measures are needed to show this.

7.3.9.4 What predicts corticosteroid induced psychiatric illness.

This study has shown that long term corticosteroid use is associated with depression but that there is no dose relationship between corticosteroids and mania. What are the genetic or endocrinological predisposing factors which mediate these associations? Genes such as the Glucocorticoid receptor gene, mineralocorticoid gene or BDNF may play a role in this group?

7.3.9.5 Where can anti TNF immunoglobulins be used in psychiatric practice

Given the emerging literature demonstrating the antidepressant action of these medications, in which patient subgroups can this medication be used?

7.4 Conclusion

The ISA study sought to look at the complex relationships between physical illness, medications and psychiatric phenotype. It has shown that socio demographic factors, disease factors and medication all exist as independent risk factors for depression and anxiety in this group. The study has been powered to demonstrate the independence of these factors and as such has achieved its main aims. The findings call for a more substantial role of psychiatric involvement in the care of patients with physical illness. Importantly there are key target areas such as corticosteroid medication which psychiatrists may consider as methods of improving patient care. Disappointingly the study was not consistent with the emerging area of psycho immunology. As stated above this may be due to the lack of sensitive measures but may also be due to either a ceiling effect of other factors or that the variance accounted for by immunology is in fact small.

The study hopes to support and develop the role of liaison psychiatry as a clinical specialty. The skills of a psychiatrist lie, in part, in gaining a good history from the patient. That physical symptoms and psychiatric symptoms are closely related, suggest that a comprehensive medical history may eliminate the need for increased and unnecessary investigations and hopefully unnecessary treatments. A liaison psychiatrist is well placed to coordinate the biological, psychological and social elements of a patients care. Thus, the importance of social predictors of depression and the need to understand the importance of loss of role is a function which psychiatry or indeed psychology can help with. It was hoped that psychoimmunology could allow psychiatrists a greater role in understanding depression in IBD as the cerebral component of a multisystemic illness. While this has not happened in

this study, the finding that anti TNF immunoglobulins can have antidepressant action is a starting point. Along with the findings about corticosteroids, this suggests that psychiatry (and not just psychology) may have an active role in the management of chronic medical illness.

If the gastroenterological teams of the future can be comprised of psychiatrists and psychologists, this may lead firstly to the better detection and treatment of mental health but the subsequent improvement in physical health care. The recent call for parity of esteem between physical and mental health care and the call for increased liaison psychiatry services in general hospitals are both consistent with the findings of this thesis.

Such development of services has commenced in oncology and diabetes and this work hopefully supports the need for commensurate services in IBD. Studies in oncology and diabetes have shown that therapeutic interventions are feasible and conclusively lead to not only improved mental but also physical health care outcomes.

In conclusion, it is hoped that the ISA study will add to existing literature on psychoimmunology, support the role of liaison psychiatry in medical teams and ultimately lead to an improvement in the physical and mental health of patients with Inflammatory Bowel Disease.

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